National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Head and Neck Cancers

Version 2.2018 — June 20, 2018

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Head and Neck Cancers

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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/clinicians.html.

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 2.2018 of the NCCN Guidelines for Head and Neck Cancers from Version 1.2018 include:

ST-15
- **Staging table added.**

MS-1
- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2018 of the NCCN Guidelines for Head and Neck Cancers from Version 2.2017 include:

Global Changes
- **The term "extracapsular spread" has been changed to "extranodal extension."**
- **"Multimodality clinical trials" has been changed to "clinical trials."**
- **"Lymphovascular invasion" has been changed to "vascular/ lymphatic invasion."**
- **For those with positive margins after resection, the adjuvant therapy option of re-resection has been revised to "re-resection *if feasible*," and the following footnote has been removed: "Consider re-resection to achieve negative margins, if feasible."**

TEAM-1
- **Under Multidisciplinary Team**
  - **Seventh bullet revised: "Physical medicine and rehabilitation *(including therapy for lymphedema of the neck)*"**
  - **Twelfth bullet revised: "Diagnostic *and interventional* radiology"**

Cancer of the Lip

LIP-2
- **Treatment of Primary and Neck**
  - **The following has been moved from the primary therapy algorithm to a footnote: "Elective neck dissection not recommended."**
  - **The following option and subsequent pathway have been removed: "Consider resection of primary ± sentinel lymph node (SLN) biopsy (category 2B)"**
- **Following surgical resection, a new pathway has been added for those with perineural/vascular/ lymphatic invasion, and RT is the recommended adjuvant therapy.**

LIP-3
- **Observation has been added as an adjuvant therapy option for patients with one positive node without adverse features.**
- **For those with extranodal extension and/or positive margins, the adjuvant therapy option of re-resection has been revised to "re-resection *if feasible (for positive margin only)*" and the following footnote has been removed: "Consider re-resection to achieve negative margins, if feasible."**

LIP-4
- **Following therapy with definitive RT or systemic therapy/RT, imaging recommendations have been revised: "FDG-PET/CT *(preferred) of primary and neck or CT of neck (with contrast).***

Cancer of the Oral Cavity

OR-2
- **First and second primary therapy options combined: "Resection of primary (preferred) ± ipsilateral (guided by tumor thickness) or bilateral (guided by location of primary) neck dissection *or SLN biopsy*"**
- **Adjuvant therapy revised for those with extranodal extension ± positive margins: "Systemic therapy/RT ~~(preferred)~~ (category 1)"**

OR-3
- **Adjuvant therapy revised for those with extranodal extension ± positive margins: "Systemic therapy/RT ~~(preferred)~~ (category 1) ~~or RT~~"**
- **For those with positive margins, the adjuvant therapy options have been revised to "Systemic therapy/RT (category 1) or re-resection *if feasible* and consider RT if negative margins ~~or RT~~."**

OR-A (1 of 2)
- **The following dose has been moved down, below concomitant boost accelerated RT: "66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)." (Also on ORPH-A, HYPO-A, GLOT-A, SUPRA-A, ETHM-A, MAXI-A, ADV-A)**

Continued

Cancer of the Oropharynx

ORPH-1

- Workup
  - First bullet revised: "Tumor human papillomavirus (HPV) testing *by p16 immunohistochemistry (IHC)* ~~recommended~~ required"
  - Fifth bullet revised: "~~Consider~~ FDG-PET/CT ~~for stage III-IV disease"~~ and moved under "as clinically indicated"
  - New pathways have been included for p16- disease versus HPV-mediated (p16+) disease.
- Footnote "g" added: "The clinical staging definitions take into consideration the new AJCC 8th edition staging for oropharynx cancer, while referencing the staging criteria previously used in clinical trials on the management of oropharynx cancer."

ORPH-2

- The following primary treatment options has been revised:
  - "Transoral or open resection of primary ± ~~ipsilateral or bilateral~~ neck dissection."
  - "For *T1*-T2, N1 only, RT + systemic therapy (category 2B for systemic therapy)."
- "Consider" removed for "systemic therapy/RT" for positive margins and other risk features. (Also on ORPH-3/4)
- Footnote removed: "The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified." (Also on ORPH-3/4)

ORPH-3

- Footnote removed: When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A). (Also on ORPH-4)

ORPHPV-1 through **ORPHPV-3**

- Pages have been added with pathways for HPV-mediated (p16+) disease.

ORPH-A 1 of 2

- The last line has been revised: "Either IMRT *(preferred)* or 3D conformal RT is recommended..." (Also on ORPH-A, 2 of 2)

ORPH-B

- This page has been added, titled "Principles of p16 Testing for HPV-Mediated Oropharyngeal Cancer."

Cancer of the Hypopharynx

HYPO-1

- Under clinical stage, the first option revised: ~~Most~~ Amenable to larynx-preserving [conservation] surgery *(Most* T1, N0, *and* selected T2, N0) ~~(amenable to larynx-preserving [conservation] surgery)~~
- Second clinical staging pathway redefined: "T1-*3, any* N ~~T2-3, Any N~~"
- Footnote removed: "Anatomical imaging is also recommended."

HYPO-2

- Second primary treatment option revised: "Surgery: Partial laryngopharyngectomy (open or endoscopic) + ipsilateral or bilateral neck dissection, + *hemithyroidectomy, and pretracheal and ipsilateral paratracheal lymph node dissection"*

HYPO-3

- Primary treatment option revised: "Partial or total laryngopharyngectomy + neck dissection, ~~including level VI, +~~ *thyroidectomy and pretracheal and ipsilateral paratracheal lymph node dissection*"

HYPO-5

- Primary treatment option revised: "~~Surgery~~ *Total laryngopharyngectomy* + neck dissection + *hemi- or total thyroidectomy,* ~~and pretracheal and~~ *after ipsilateral or bilateral paratracheal lymph node dissection"*

Cancer of the Nasopharynx

NASO-1

- Sixth bullet revised: "Imaging for distant metastases with FDG-PET/CT and/or chest CT with contrast~~, especially for nonkeratinizing histology, endemic phenotype, or N2-3 disease; may be considered for stage III-IV disease~~"

NASO-2

- Under primary treatment for T1, N1-3; T2-T4, any N, the category 3 has been removed from the option of induction chemotherapy ~~category 3~~ followed by chemo/RT. (Also on CHEM-A, 1 of 5)

NASO-A

- Last line revised: "*Either* IMRT ~~is~~ (preferred) *or* ~~over~~ 3D conformal RT *is recommended* ~~in~~ *for* cancers of the nasopharynx to minimize dose to critical structures. *Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.*"

Continued

Cancer of the Glottic Larynx

GLOT-1

- Under workup, last bullet revised: "~~Consider~~ Pulmonary function ~~tests~~ *evaluation* for conservation surgery candidates."

GLOT-3

- For N0,N1 disease after surgery, the following line has been added to the primary treatment options: "...*and pretracheal and ipsilateral paratracheal lymph node dissection."*

GLOT-4

- After surgery, option revised: "Laryngectomy with thyroidectomy, ~~as indicated,~~ ipsilateral ~~central,~~ or bilateral neck dissection*, and pretracheal and ipsilateral paratracheal lymph node dissection*"

GLOT-5

- For primary site < PR, "surgery" changed to "laryngectomy."

GLOT-6

- The following line has been added to the primary treatment options for N0, N1, and N2-3 disease: "...*and pretracheal and ipsilateral paratracheal lymph node dissection."*
- After primary treatment, pathways have been added to define the adjuvant therapy options for those with adverse features, and those with no adverse features.

Cancer of the Supraglottic Larynx

SUPRA-2

- For positive margin, the adjuvant therapy option of re-resection has been revised to: "Re-resection *if feasible, in highly selected patients*"

Ethmoid Sinus Tumors

ETHM-2

- Footnote "l" revised: "Adverse features include positive margins, *high-grade lesions*, and intracranial extension (See Discussion)."

ETHM-3

- Following incomplete resection and no residual disease:
  - The following primary treatment option has been revised: "Surgery, if feasible ~~(See newly diagnosed T1,T2)~~."
  - The following adjuvant therapy option has been added for those after primary treatment with surgery: "*Consider systemic therapy/RT (category 2B) if adverse features."*

ETHM-A

- Last line revised: "*Either* IMRT ~~is~~ (preferred) *or* ~~over~~ 3D conformal RT *is recommended* for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. ~~The role of proton therapy is being investigated.~~ *Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy."* (Also on MAXI-A)

Maxillary Sinus Tumors

MAXI-1

- Footnote "g" revised: "For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider *a clinical trial and* referral to a major medical center that specializes in these diseases." (Also on ETHM-1)

MAXI-3

- Footnote removed: "For surgical resection, consider preoperative RT or preoperative systemic therapy/RT in select patients (category 2B)."

Very Advanced Head and Neck Cancer

ADV-2

- For PS 0-1, the following primary treatment remains an option but has been removed from this page since it is included in the combination therapy options listed on CHEM-A (2 of 5): "Platinum + 5-FU + cetuximab (category 1)." (Also on ADV-4)

ADV-3

- The primary treatment options have been revised for those with a locoregional recurrence without prior RT, if resectable: Surgery or *Concurrent* systemic therapy/RT or *Induction chemotherapy (category 3) followed by RT or systemic therapy/RT*
- Footnote "c" added: "When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A)."

Continued

ADV-A (1 of 2)
- Line added to the chemoradiation section: "Data indicate that accelerated fractionation does not offer improved efficacy over conventional fractionation."
  - Ang K, Zhang Q, Wheeler RH, et al. A phase III trial (RTOG 0129) of two radiation-cisplatin regimens for head and neck carcinomas (HNC): Impact of radiation and cisplatin intensity on outcome [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 5507.
  - 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.
- Footnote "2", line added: "*Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)"*

Occult Primary

OCC-1
- Under workup, fourth bullet revised: "HPV, Epstein-Barr virus (EBV) testing ~~suggested~~ for squamous cell or undifferentiated histology"

OCC-2
- Definitive treatment revised following evaluation of level IV or V adenocarcinoma of neck node for intraclavicular primary: "Neck dissection if indicated ± *adjuvant treatment if indicated (see OCC-4).* Also, a link has been added to FOLL-A after treatment."

OCC-3
- Indications have been revised for the following treatment options:
  - "~~Surgery~~ *Neck dissection* (preferred for N1 disease, *single node ≤3 cm*)"
  - "RT for N1, *single node ≤3 cm* (category 2B)"
  - "Induction chemotherapy *for N2-3* (category 3) followed by systemic therapy/RT or RT"

Salivary Gland Tumors

SALI-3
- Cancer site descriptors have been revised:
  - *Major salivary gland (*parotid, *submandibular, sublingual)*
  - *Minor salivary gland ~~Sites~~*
- Treatment option revised for majory salivary gland, clinical N0: "~~Parotidectomy~~ *Surgery* with complete resection of tumor ± neck dissection for high-grade and/*or T3-4* ~~high-stage~~ tumors"
- Treatment option revised for majory salivary gland, clinical N1: "~~Parotidectomy~~ *Surgery* + neck dissection"
- Added "T3-4 tumors" to list of adverse features after complete resection of a major salivary gland tumor.
- Adjuvant treatment options revised if adverse features after complete resection of a major salivary gland cancer: "Adjuvant RT ~~(preferred)~~ or ~~consider~~ systemic therapy/RT (category 2B)"

SALI-4
- The following recurrence therapy options have been added for those with distant metastases and PS 0-3:
  - "Androgen receptor therapy (ie. leuprolide, bicalutamide) if AR+
  - Trastuzumab if HER2+ (category 2B)"
- Footnote "m" added: "Check androgen receptor (AR) status and HER2 status prior to treatment for distant metastases."

SALI-A
- Last line added: "Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy."
- Footnote "2" revised: "~~Neutrons are still used in selected patients.~~ *Neutron therapy was historically considered a promising solution for unresectable salivary gland cancers, but this therapy is currently offered at only one center in the United States.* Pfister DG, et al..."

Continued

SALI-A (continued)

- Footnote "5" added: In general, the reirradiated population of head and neck cancer patients described in 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. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)"

Mucosal Melanoma

MM-1

- Workup, fifth bullet revised: "Consider FDG-PET/CT ~~scan~~ *or chest/abdominal/pelvic CT with contrast,* and brain MRI (with and without contrast) to rule out metastatic disease"

MM-2

- "Wide surgical resection" changed to "surgical resection." (Also on MM-3)

MM-3

- Primary treatment options revised for stage III disease: "~~Wide~~ surgical resection, ~~elective~~ + neck dissection"

MM-4

- Additional therapy revised after nodal dissection: "± RT to nodal bed *for high-risk features"*
- Footnote "f" added: "High-risk, adverse features: >2 nodes, single node >3 cm, extranodal extension, recurrence in nodal basin after previous surgery."

MM-A

- Last two lines added: "Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy."

Follow-Up Recommendations

FOLL-A (1 of 2)

- First line revised: "H&P exam (including a complete head and neck exam; *and* mirror and fiberoptic examination ~~as clinically indicated~~)"
- Imaging recommendations have been grouped together.

FOLL-A (2 of 2)

- Response after systemic therapy/RT or RT
  - First bullet revised under assess extent of disease or distant metastases: "FDG-PET/CT ~~(including CT + IV contrast)~~ at minimum 12 wk"
  - Added after FDT-PET/CT: "*If imaging is positive, CT of primary and neck or MRI with contrast*"

Principles of Surgery

SURG-A (3 of 8)

- Added to fifth bullet: "*If carcinoma in situ is present and if additional margins can be obtained that is the favored approach. Carcinoma in situ should not be considered an indication for concurrent postoperative chemoradiation."*

SURG-A (5 of 8)

- Under neck management, first bullet revised: "Tumor sites that frequently have bilateral lymphatic drainage (eg, base of tongue, palate, supraglottic larynx, *hypopharynx, nasopharynx,* deep pre-epiglottic..."
- Line revised: "Patients with advanced lesions involving the anterior tongue, floor of the mouth, or ~~lip~~ *alveolus* that approximate or cross the midline should undergo contralateral ~~submandibular~~ *selective/modified neck* dissection as necessary to achieve adequate tumor resection."

SURG-A (6 of 8)

- First bullet revised: "...Elective dissection depends on primary tumor extent and site. ~~Subglottic laryngeal cancers are sites where elective level VI dissections are often~~ *For advanced glottic and hypopharyngeal cancers treated with primary surgery, a level VI dissection (including pretracheal lymph nodes, the delphian lymph node, and unilateral or bilateral paratracheal lymph nodes) and hemithyroidectomy to total thyroidectomy is appropriate. For primary subglottic tumors or glottic cancers with significant subglottic extension, a level VI dissection with unilateral or total thyroidectomy is* considered appropriate *based on the extent of the primary tumor. For example a T4a glottic tumor with extension through the cricothyroid membrane and subglottic extension should include a total thyroidectomy, and pretracheal and bilateral paratracheal lymph node dissection. Parathyroid glands should be preserved in situ or auto transplanted as indicated."*

Continued

Updates in Version 1.2018 of the NCCN Guidelines for Head and Neck Cancers from Version 2.2017 include:

Radiation Techniques

RAD-A (2 of 5)

- Under IMRT, PBT and Fractionation, dosing revised in second sentence: The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (66–72 ~~74~~ Gy to gross disease; ~~50–60~~ *44–63* Gy to subclinical disease) for each fraction..."
- Last line added under proton beam therapy: "*Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.*"

RAD-A (3 of 5)

- First heading revised: Palliative Radiation *3D Conformal RT, IMRT, and SBRT*
- Seventh bullet added under reirradiation: "*For 3D conformal RT and IMRT: Standard dosing is 59.4–60 Gy at 1.8–2 Gy/fraction. Hyperfractionated schedule is 60 Gy at 1.2–1.5 Gy/fraction.*"

Principles of Systemic Therapy

CHEM-A (1 of 5)

- Second bullet revised: "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 *in* 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.~~"
- Third sub-bullet revised under induction/sequential chemotherapy for cancer of the Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary: "Following induction, agents ~~to be~~ used with concurrent chemoradiation typically include weekly carboplatin*, weekly cisplatin (category 2B),* or *weekly* cetuximab."

CHEM-A (2 of 5)

- Gemcitabine/vinorelbine has been removed from the options for nasopharyngeal cancer.
- Cisplatin/gemcitabine has been changed from a category 2A to a category 1 recommendation for recurrent, unresectable or metastatic nasopharyngeal cancer.
- New headings have been added to identify the first-line therapy options and second-line/subsequent therapy options.
- Pembrolizumab has been added as a category 2B, second-line therapy option for nasopharyngeal cancer, if previously treated, PD-L1-positive recurrent or metastatic disease.

CHEM-A (3 of 5) through CHEM-A (5 of 5)

- References have been updated.

Principles of Nutrition

NUTR-A (1 of 2)

- New section added for pain management with the following bullet and references: Assess pain from oral mucositis and prescribe gabapentin or doxepin as clinically indicated.
  - ◊ Bar Ad V, Weinstein G, Dutta PR, et al. Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy. Cancer 2010;116:4206-4213.
  - ◊ Leenstra JL, Miller RC, Qin R, et al. Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32:1571-1577.

Staging

ST-1

- Staging tables have been updated to reflect the AJCC 8th Edition Cancer Staging System.

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 (including therapy for lymphedema of the neck)
- Speech and swallowing therapy
- Clinical social work
- Clinical nutrition
- Pathology (including cytopathology)
- Diagnostic and interventional 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 (See NCCN Guidelines for Smoking 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)

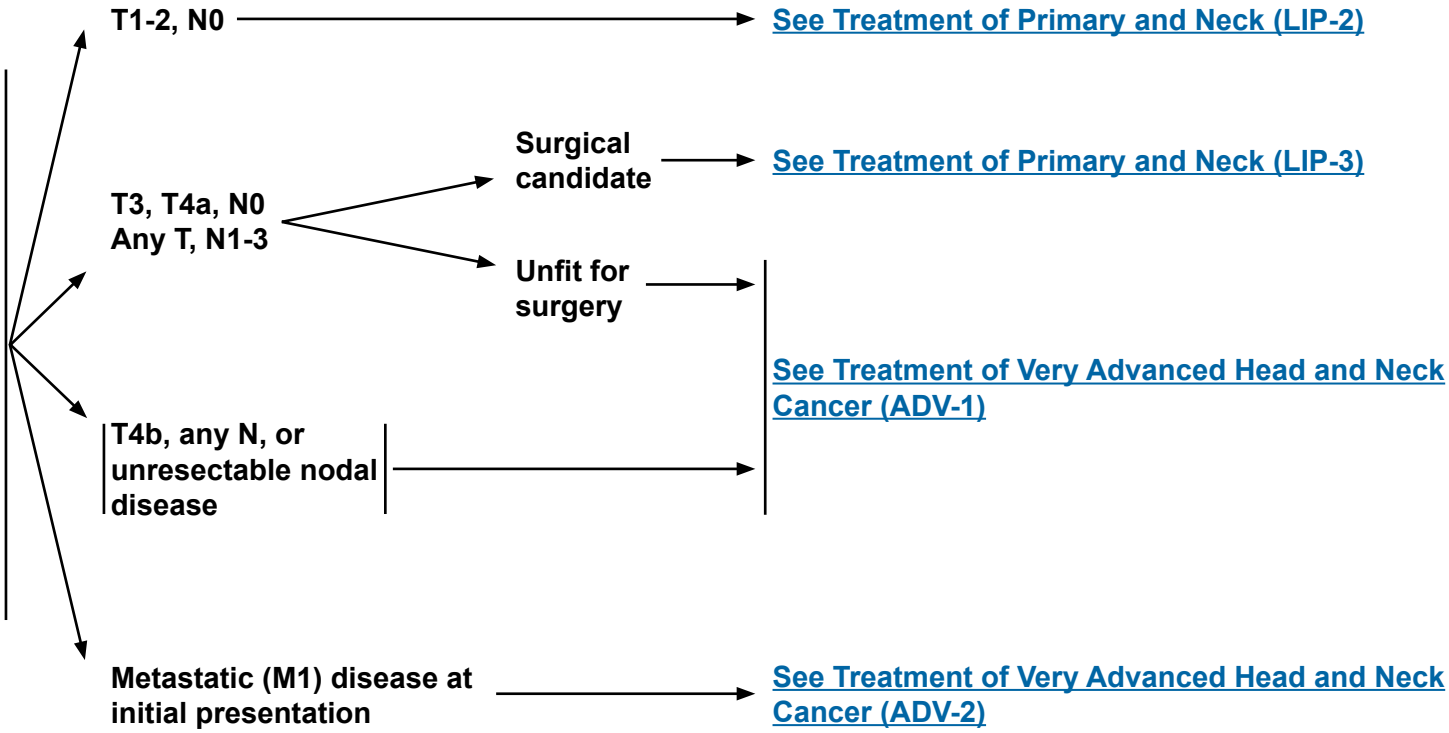
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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 CT (with or without contrast) as clinically indicated[c]
- As indicated for primary evaluation
  - Panorex
  - CT and/or MRI with contrast of primary and neck
- Preanesthesia studies as clinically indicated
- Dental evaluation[d]

Multidisciplinary consultation as indicated

CLINICAL STAGING



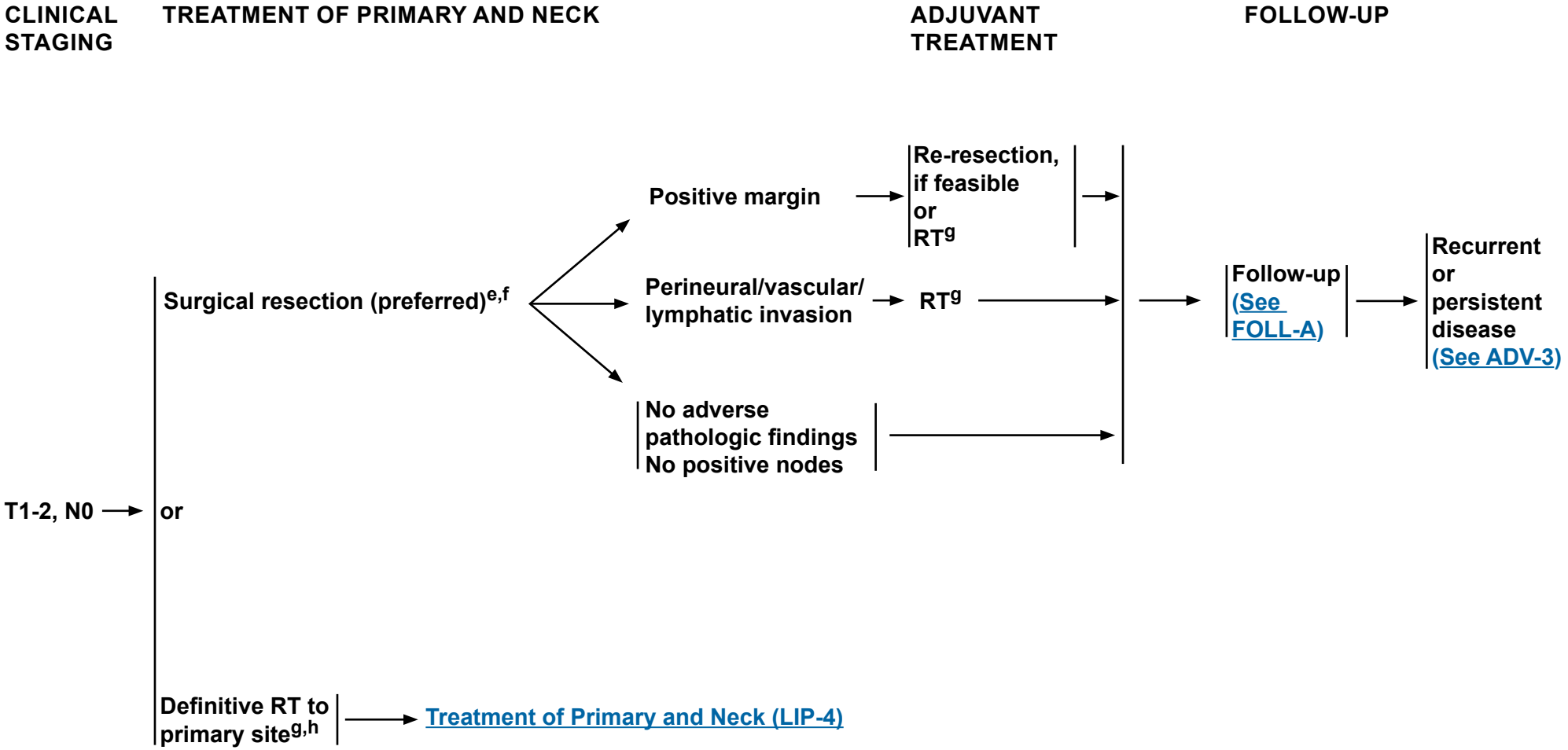
[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation 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]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

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

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



[e]Elective neck dissection is not recommended.
[f]See Principles of Surgery (SURG-A).
[g]See Principles of Radiation Therapy (LIP-A).
[h]No elective treatment to neck is preferred for the T1-2, N0.

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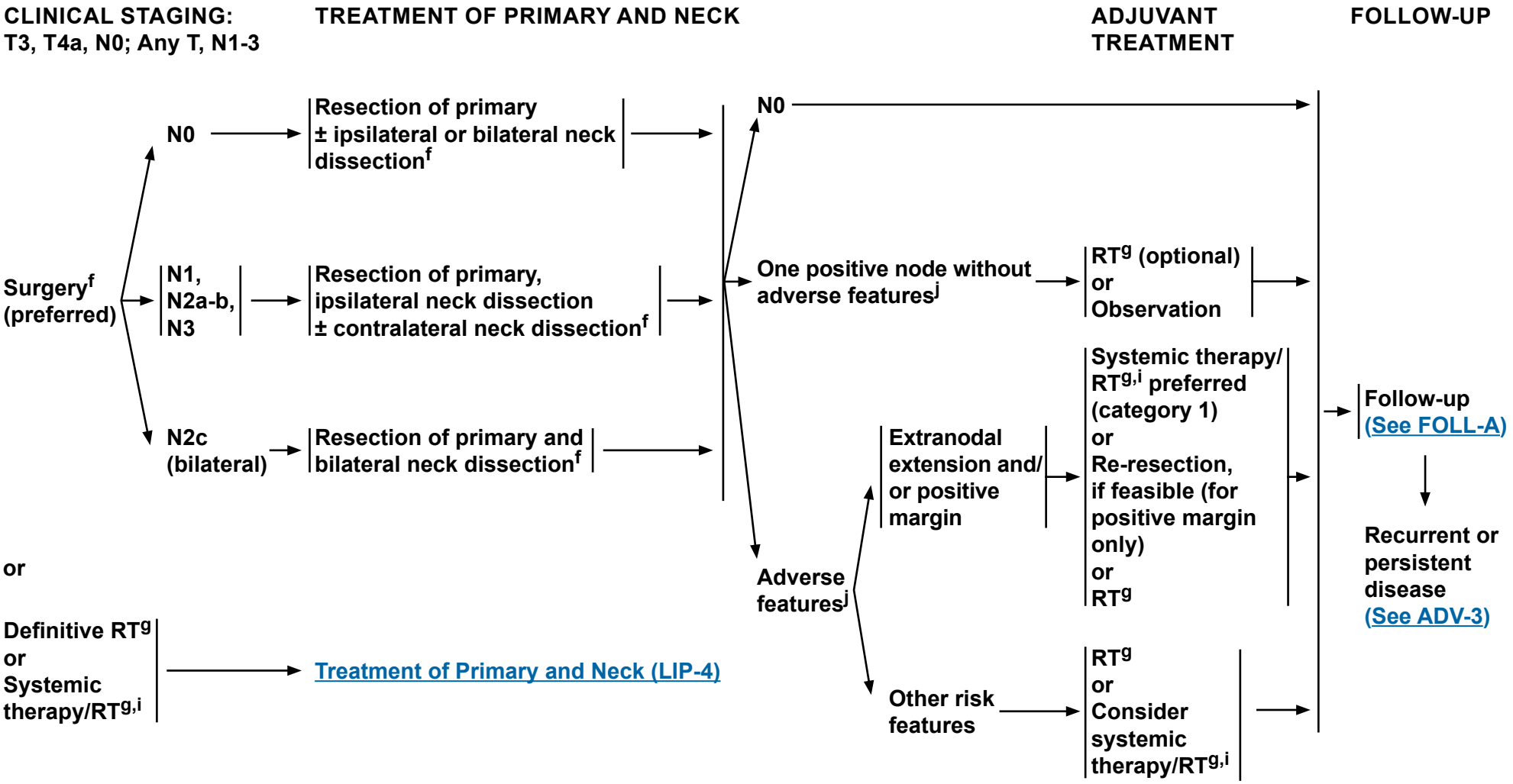
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f]See Principles of Surgery (SURG-A).
[g]See Principles of Radiation Therapy (LIP-A).
[i]See Principles of Systemic Therapy (CHEM-A).
[j]Adverse features: extranodal extension, positive margins, multiple positive nodes, or perineural/lymphatic/vascular invasion.

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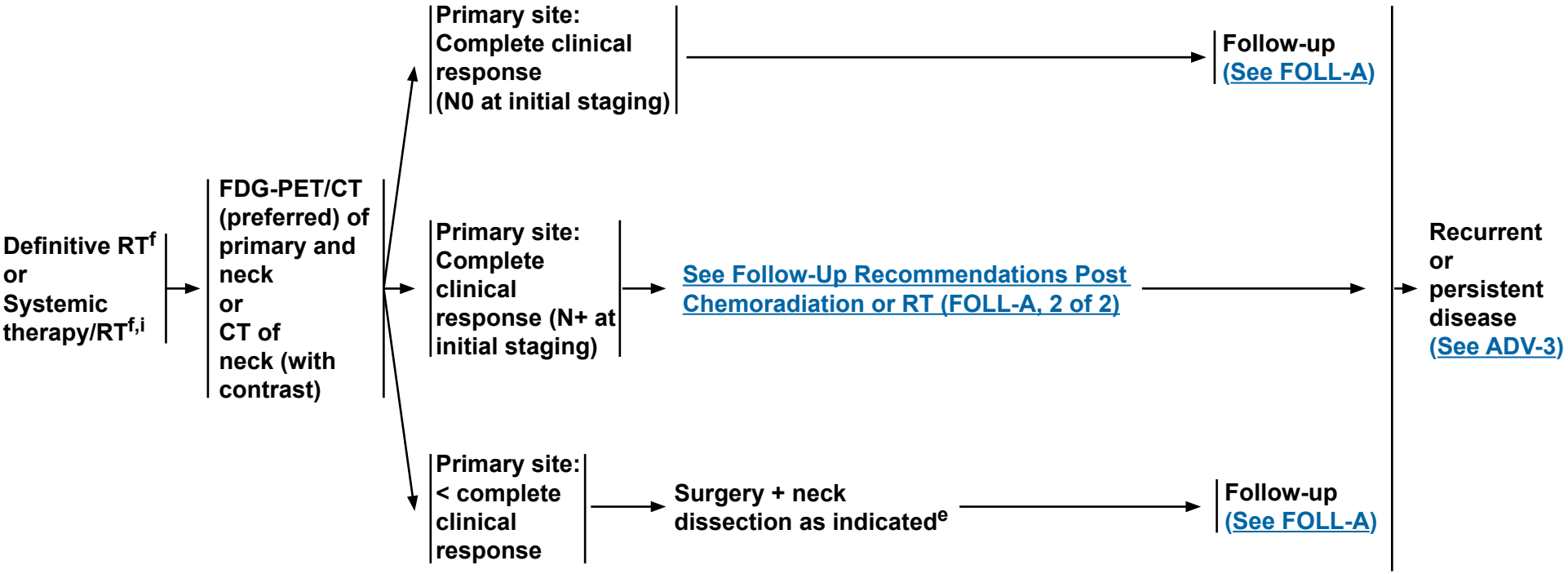
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL STAGING:
T3, T4a, N0; Any T, N1-3

TREATMENT OF PRIMARY AND NECK

FOLLOW-UP



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

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

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 j 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]
- For T1-T2 simple lesions, treat with postoperative RT as per non-melanoma skin cancers. See NCCN Guidelines for Non-Melanoma Skin Cancer

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

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

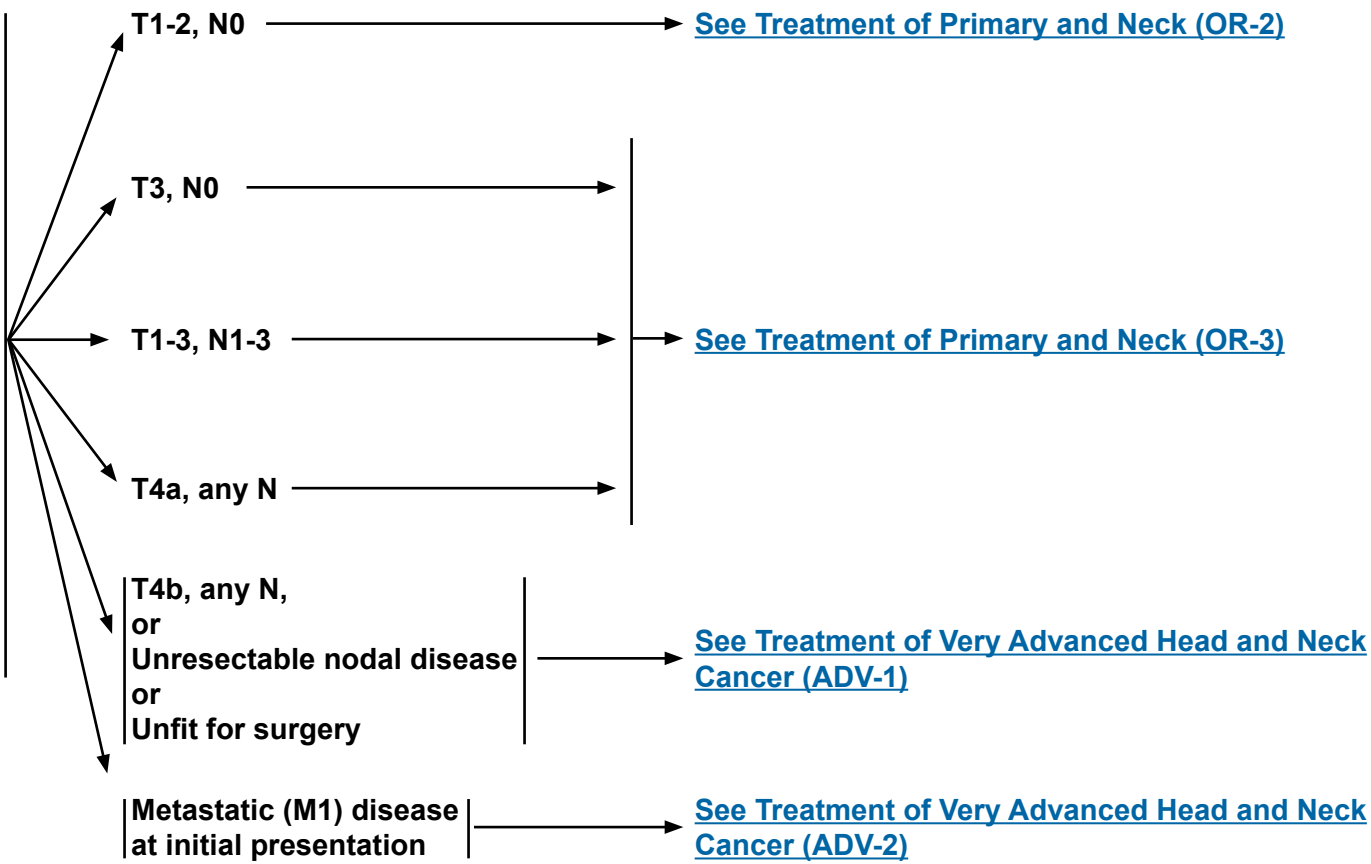
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy
- Chest CT (with or without contrast) as clinically indicated[c]
- CT with contrast and/or MRI with contrast of primary and neck as indicated
- Consider FDG-PET/CT for stage III-IV disease[d]
- Examination under anesthesia (EUA) with endoscopy, if indicated
- Preanesthesia studies as clinically indicated
- Dental/prosthodontic evaluation,[e] including Panorex or dental CT without contrast as clinically indicated
- Nutrition, speech and swallowing evaluation/therapy as indicated[f]

- 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]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

[d]See Discussion.

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

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

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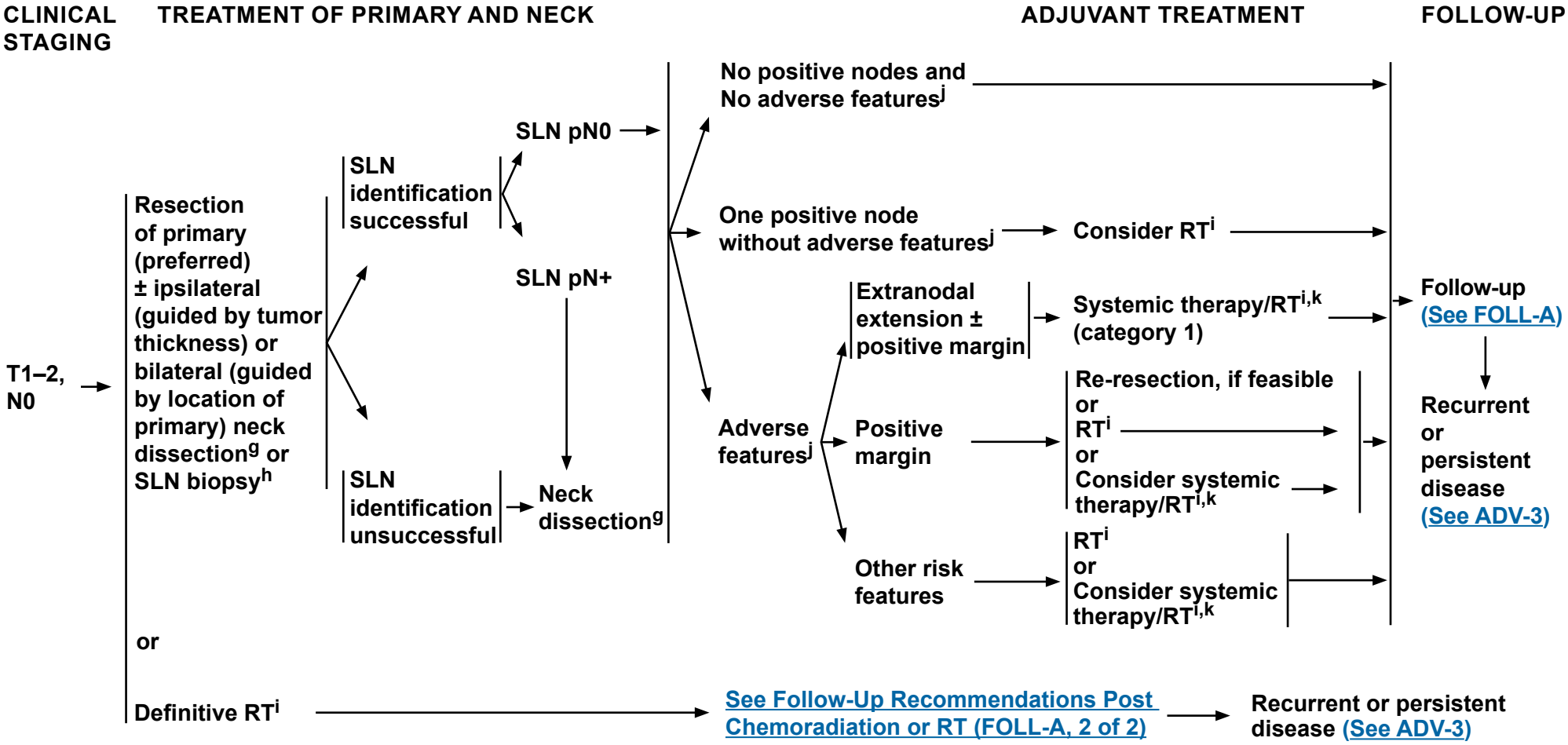
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



[g] See Principles of Surgery (SURG-A).
[h] See Sentinel Lymph Node Biopsy in Principles of Surgery [SURG-A 6 of 8].
[i] Principles of Radiation Therapy (OR-A).

[j] Adverse risk features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
[k] See Principles of Systemic Therapy (CHEM-A).

Note: All recommendations are category 2A unless otherwise indicated.
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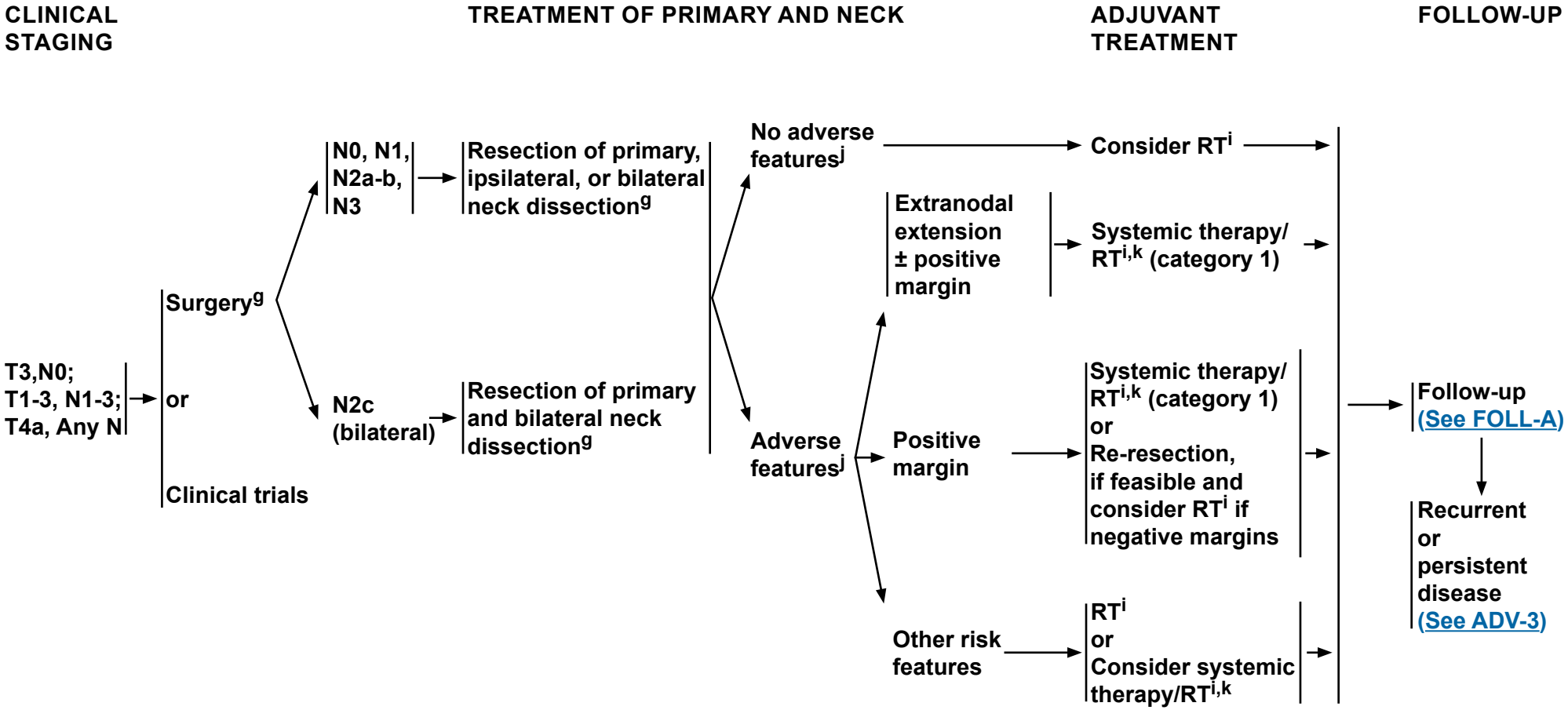
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



[g] See Principles of Surgery (SURG-A).
[i] See Principles of Radiation Therapy (OR-A).
[j] Adverse risk features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
[k] 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 patient with cancer 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 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[2]**
      - **– 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)**
        - **– 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **– 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 3D 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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 j 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 systemic therapy[6-10]**

Either IMRT or 3D 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]See Principles of Systemic Therapy (CHEM-A).
[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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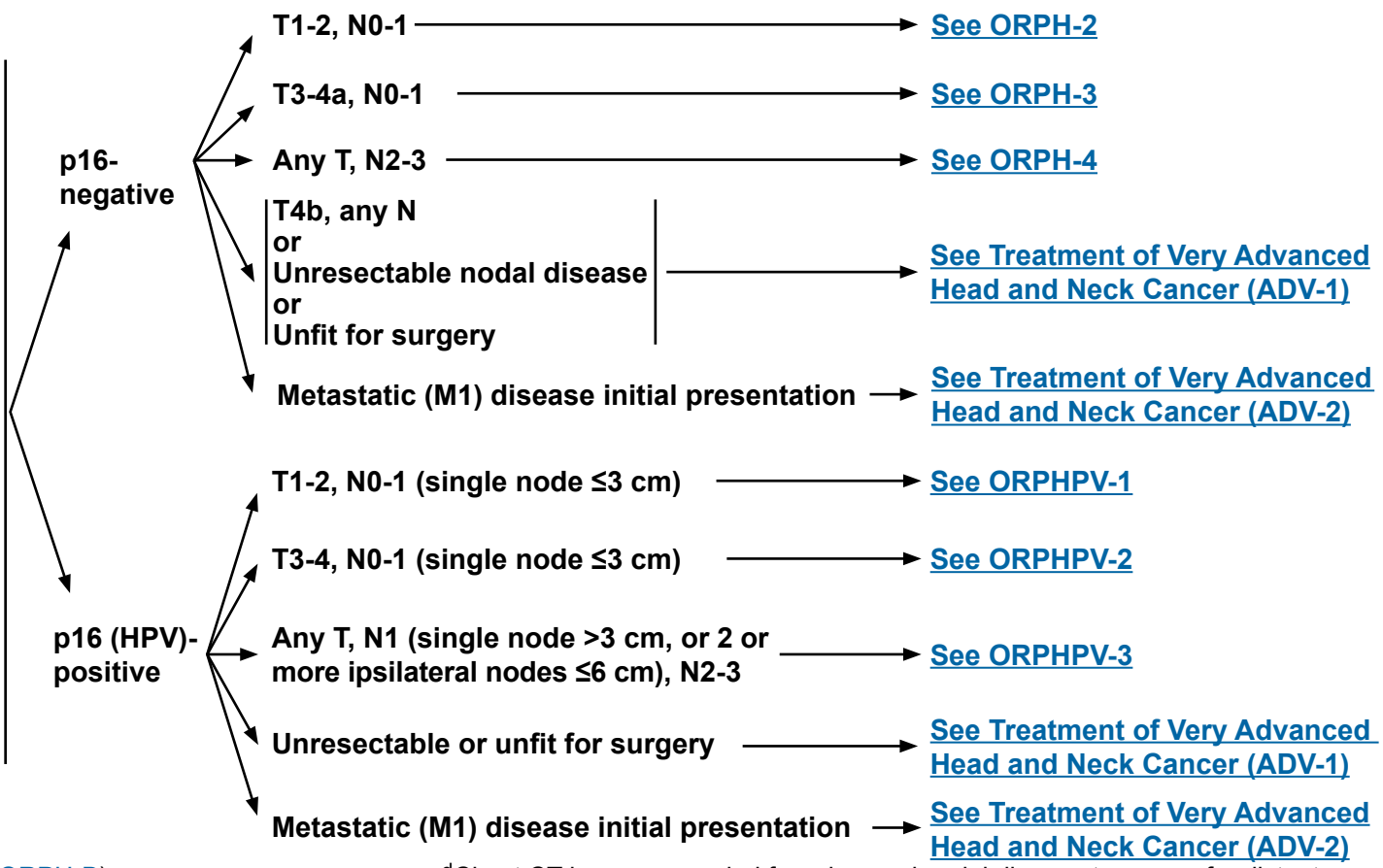
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

WORKUP

- Tumor human papillomavirus (HPV) testing by p16 immunohistochemistry (IHC) required[a]
- H&P[b,c] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy of primary site or fine-needle aspiration (FNA) of the neck
- CT with contrast and/or MRI with contrast of primary and neck
- Preanesthesia studies
- As clinically indicated:
  - FDG-PET/CT
  - Chest CT[d] (with or without contrast)
  - Dental evaluation,[e] including Panorex
  - Nutrition, speech and swallowing evaluation/therapy, and audiogram[f]
  - EUA with endoscopy

Multidisciplinary consultation as clinically indicated



[a]See Principles of p16 Testing and HPV Status (ORPH-B).

[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]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

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

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

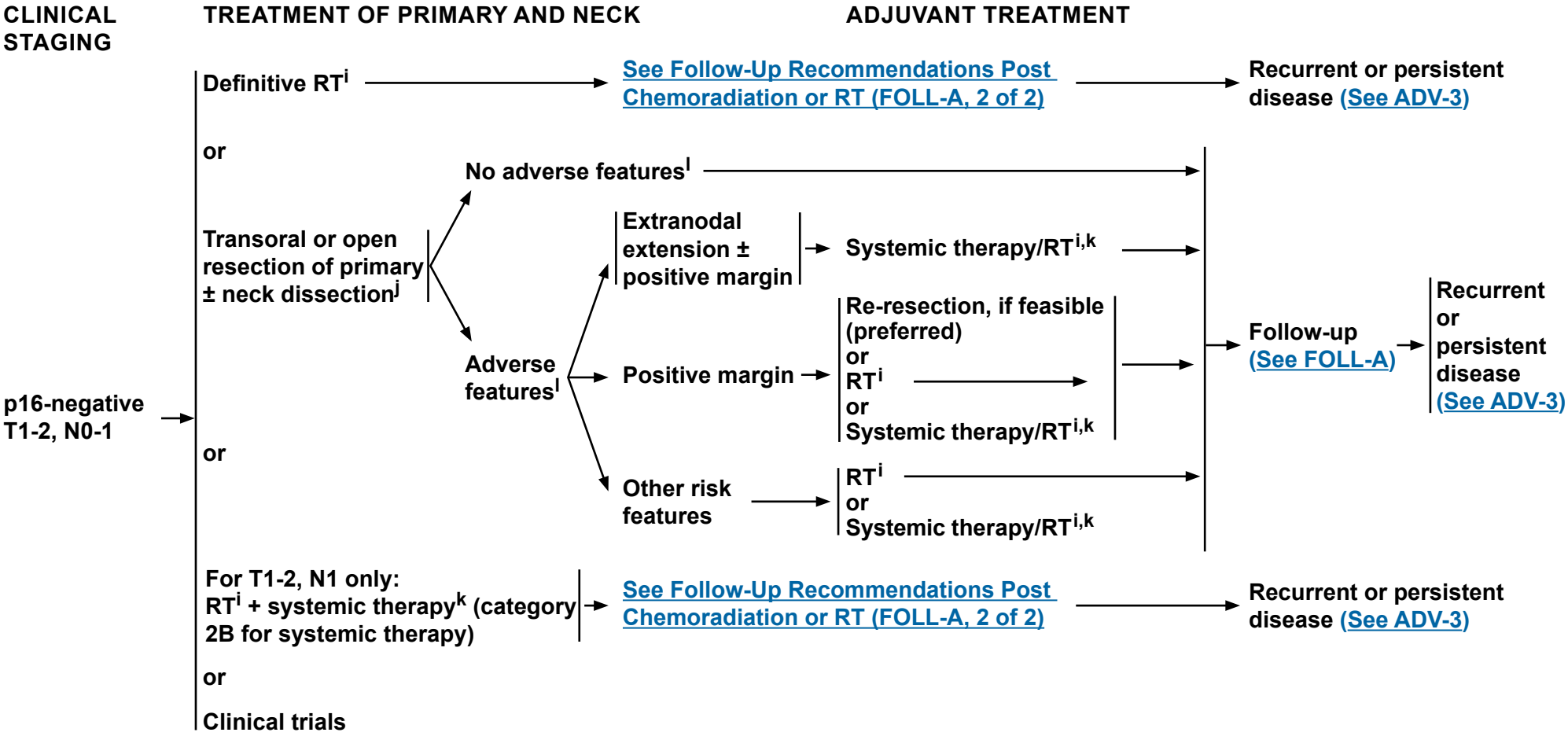
[g]The clinical staging definitions take into consideration the new AJCC 8th edition staging for oropharynx cancer, while referencing the staging criteria previously used in clinical trials on the management of oropharynx cancer.

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

NCCN Guidelines Version 2.2018
Cancer of the Oropharynx (p16-negative)

NCCN Guidelines Index
Table of Contents
Discussion

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



[i] See Principles of Radiation Therapy (ORPH-A).
[j] See Principles of Surgery (SURG-A).
[k] See Principles of Systemic Therapy (CHEM-A).
[l] Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).

Note: All recommendations are category 2A unless otherwise indicated.
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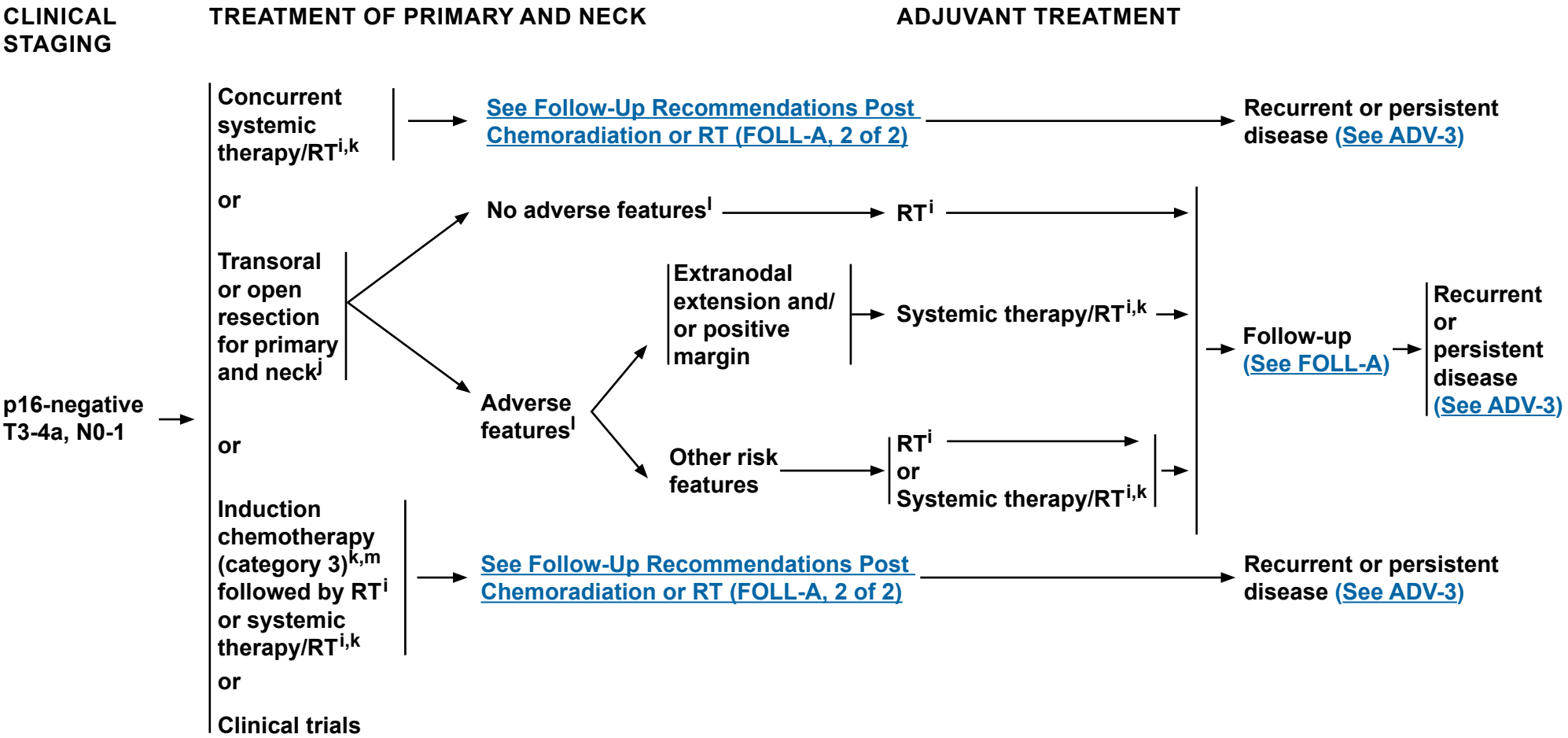
Base of tongue/tonsil/posterior pharyngeal wall/soft palate



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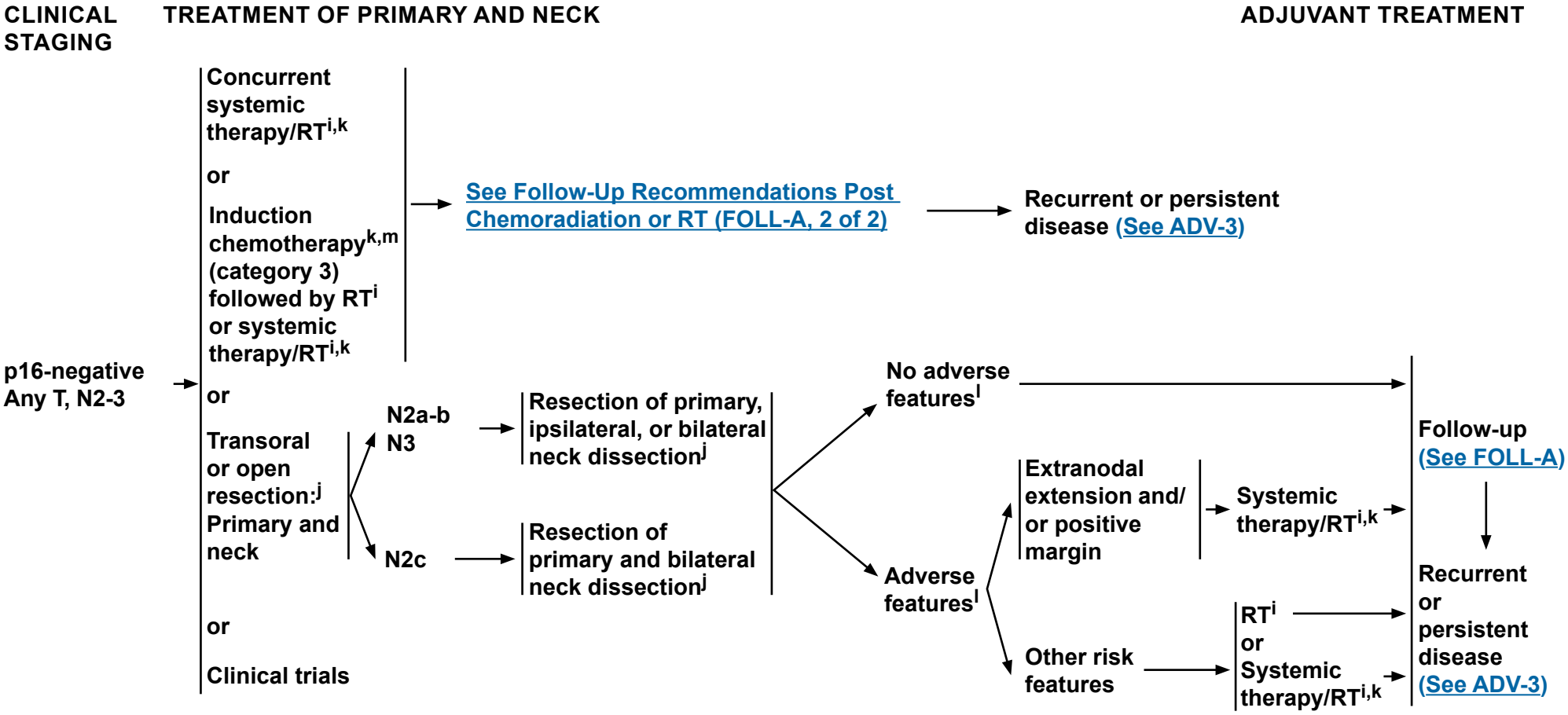
[m] See Discussion on induction chemotherapy.

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

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



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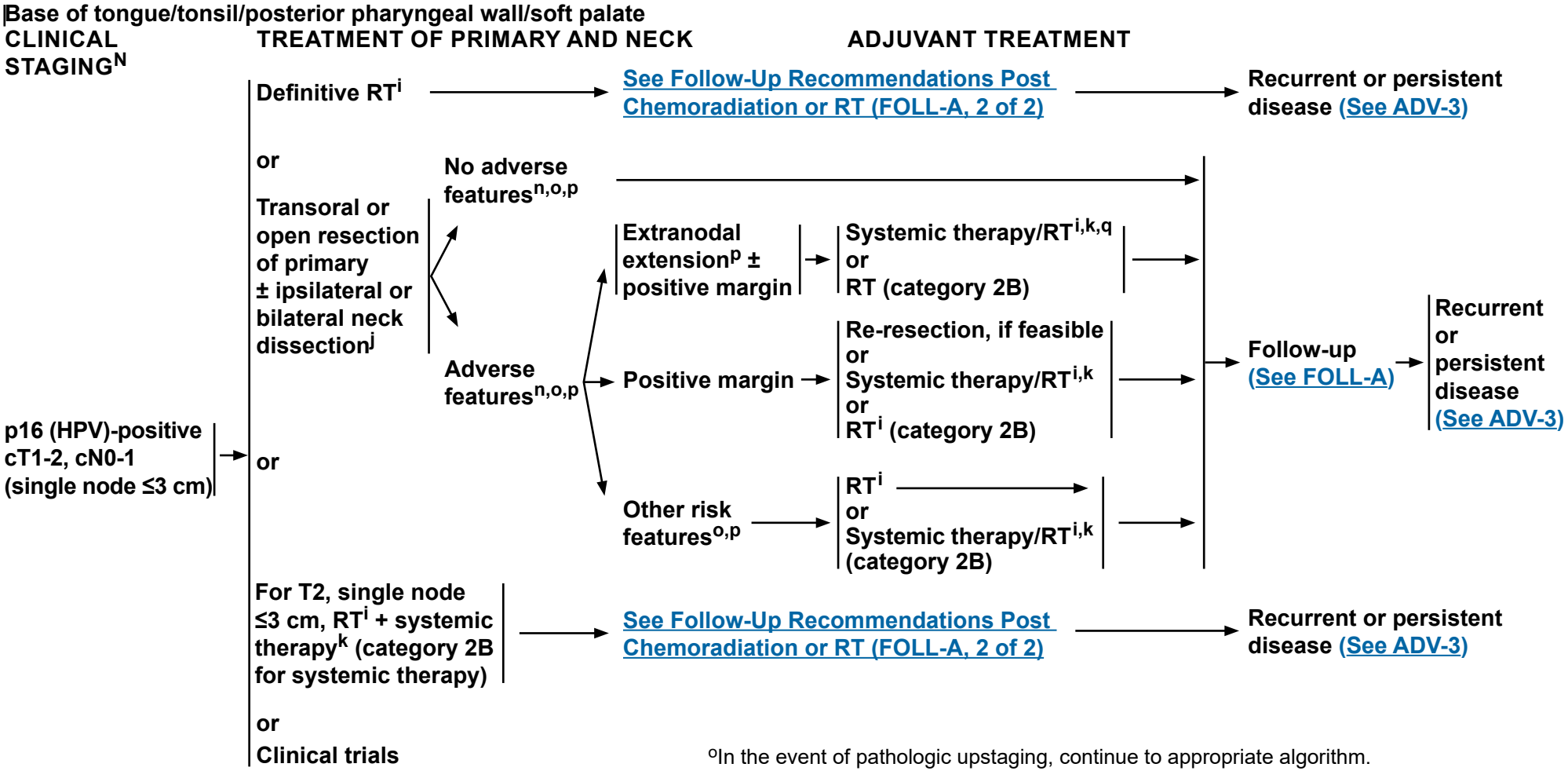
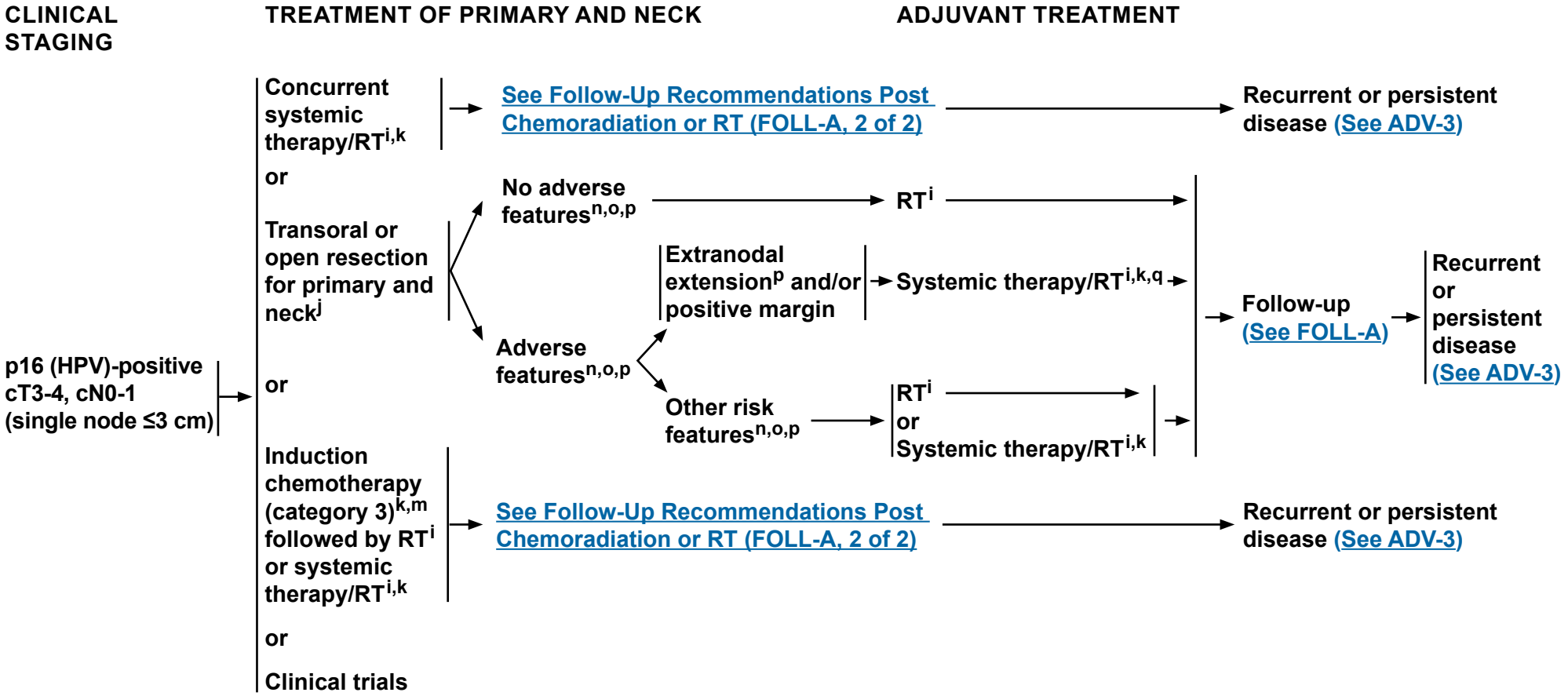


[i]See Principles of Radiation Therapy (ORPH-A).
[j]See Principles of Surgery (SURG-A).
[k]See Principles of Systemic Therapy (CHEM-A).
[n]Pathologic staging criteria differ from clinical staging criteria in HPV-mediated oropharyngeal cancer. For pathologic stage following resection, see AJCC 8th edition for appropriate staging criteria (ST-7).
[o]In the event of pathologic upstaging, continue to appropriate algorithm.
[p]Adverse features: extranodal extension, positive margins, nodal disease in levels IV or V, perineural invasion, vascular embolism, lymphatic invasion (See Discussion). The definition of an adverse feature in the context of HPV+ disease is an area of active research. This includes the presence and extent of ENE, and the number of involved nodes.
[q]The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.

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

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



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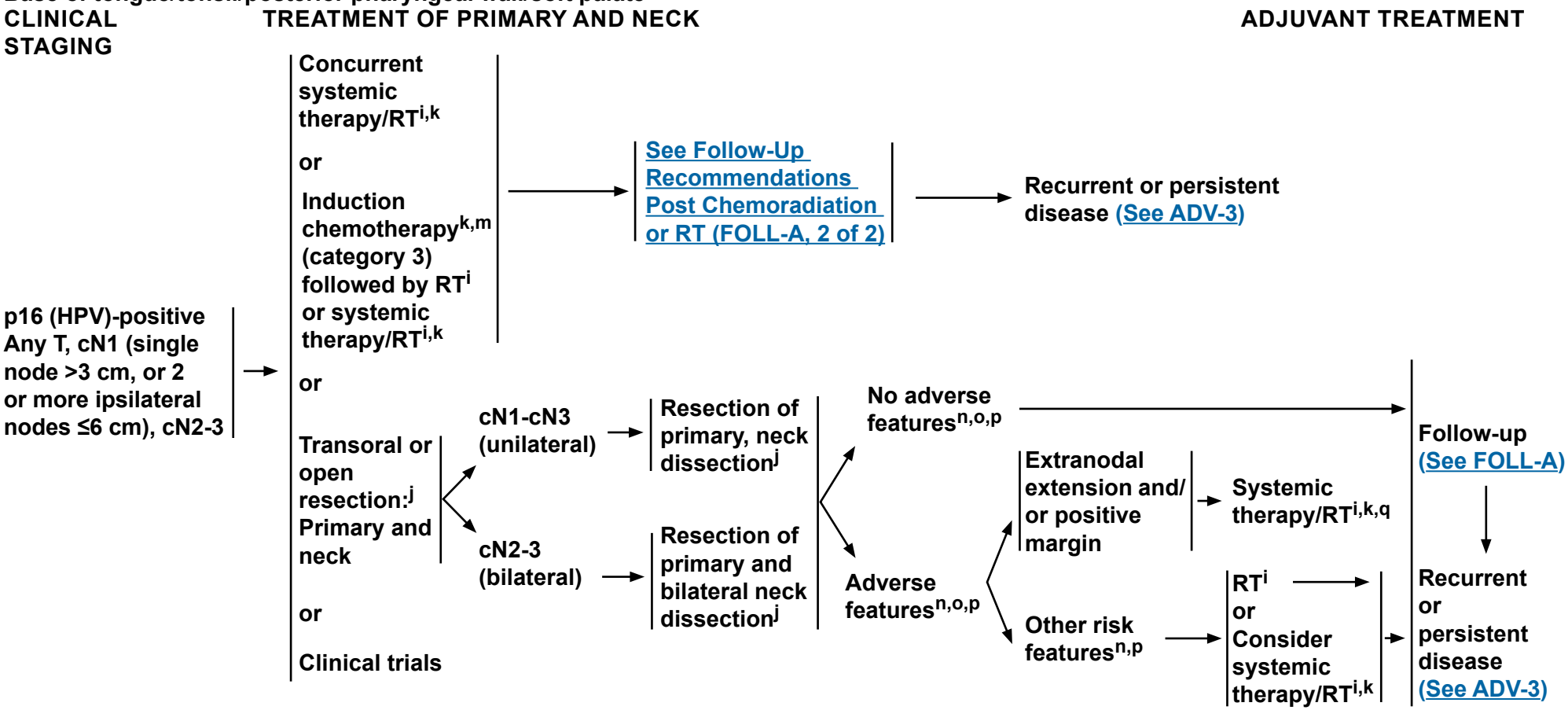
Base of tongue/tonsil/posterior pharyngeal wall/soft palate



[i] See Principles of Radiation Therapy (ORPH-A).
[j] See Principles of Surgery (SURG-A).
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[q] The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[2]**
      - **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)**
        - **66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **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]**

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]**

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures.

[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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 l 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 systemic therapy[7-11]**

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures.

[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] See Principles of Systemic Therapy (CHEM-A).
[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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PRINCIPLES OF P16 TESTING FOR HPV-MEDIATED OROPHARYNGEAL CANCER

- **P16 expression is highly correlated with HPV status and prognosis and is widely available.**
- **A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by IHC is a widely available surrogate biomarker that has very good agreement with HPV status as determined by the gold standard of HPV E6/E7 mRNA expression.[1-3] Other tests include HPV detection through PCR and in situ hybridization (ISH).[1,3]**
- **Sensitivity of IHC staining for p16 and PCR-based assay is high, although specificity is highest for ISH.[3]**
- **Due to variations in sensitivity and specificity values of testing options, multiple methods may be used in combination for HPV detection, but HPV detection through PCR and ISH may provide additional sensitivity for the former and specificity for the latter in the case of an equivocal p16 or unclear clinical scenario.[3-6]**
- **Sufficient pathologic material for HPV testing can be obtained through FNA.[6,7]**
- **A small proportion of tumors at non-oropharyngeal sites (eg, paranasal sinus, oral cavity, larynx) are HPV-related. However, given the small proportion and lack of consistent evidence in support of prognostic significance, routine HPV testing or p16 tseting of non-oropharyngeal cancers is not recommended.**
- **Guidelines for testing are available from the College of American Pathologists.[8]**

[1]Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol 2012;36:945-954.
[2]Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus–associated oropharyngeal cancers with favorable prognosis. J Clin Oncol 2006;24:736-747.
[3]Cantley RL, Gabrielli E, Montebelli F, et al. Ancillary studies in determining human papillomavirus status of squamous cell carcinoma of the oropharynx: a review. Patholog Res Int 2011;2011:138469.
[4]Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. Cancer 2010;116:2166-2173.
[5]Thavaraj S, Stokes A, Guerra E, et al. Evaluation of human papillomavirus testing for squamous cell carcinoma of the tonsil in clinical practice. J Clin Pathol 2011;64:308-312.
[6]Snow AN, Laudadio J. Human papillomavirus detection in head and neck squamous cell carcinomas. Adv Anat Pathol 2010;17:394-403.
[7]Begum S, Gillison ML, Nicol TL, Westra WH. Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 2007;13:1186-1191.
[8]Lewis JS, Jr., Beadle B, Bishop JA, et al. Human papillomavirus testing in head and neck carcinomas: Guideline from the College of American Pathologists. Arch Pathol Lab Med 2017.

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

WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and/or fiberoptic examination as clinically indicated
- Biopsy of primary site or FNA of neck
- Chest CT (with or without contrast) as clinically indicated[c]
- CT with contrast and/or MRI with contrast of primary and neck
- Consider FDG-PET/CT 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

- Amenable to larynx-preserving [conservation] surgery (most T1, N0, and selected T2, N0) → See Treatment of Primary and Neck (HYPO-2)
- Advanced cancer requiring (amenable to) pharyngectomy with total laryngectomy
  - T1-3, any N → See Treatment of Primary and Neck (HYPO-3)
  - T4a, Any N → See Treatment of Primary and Neck (HYPO-5)
- 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]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

[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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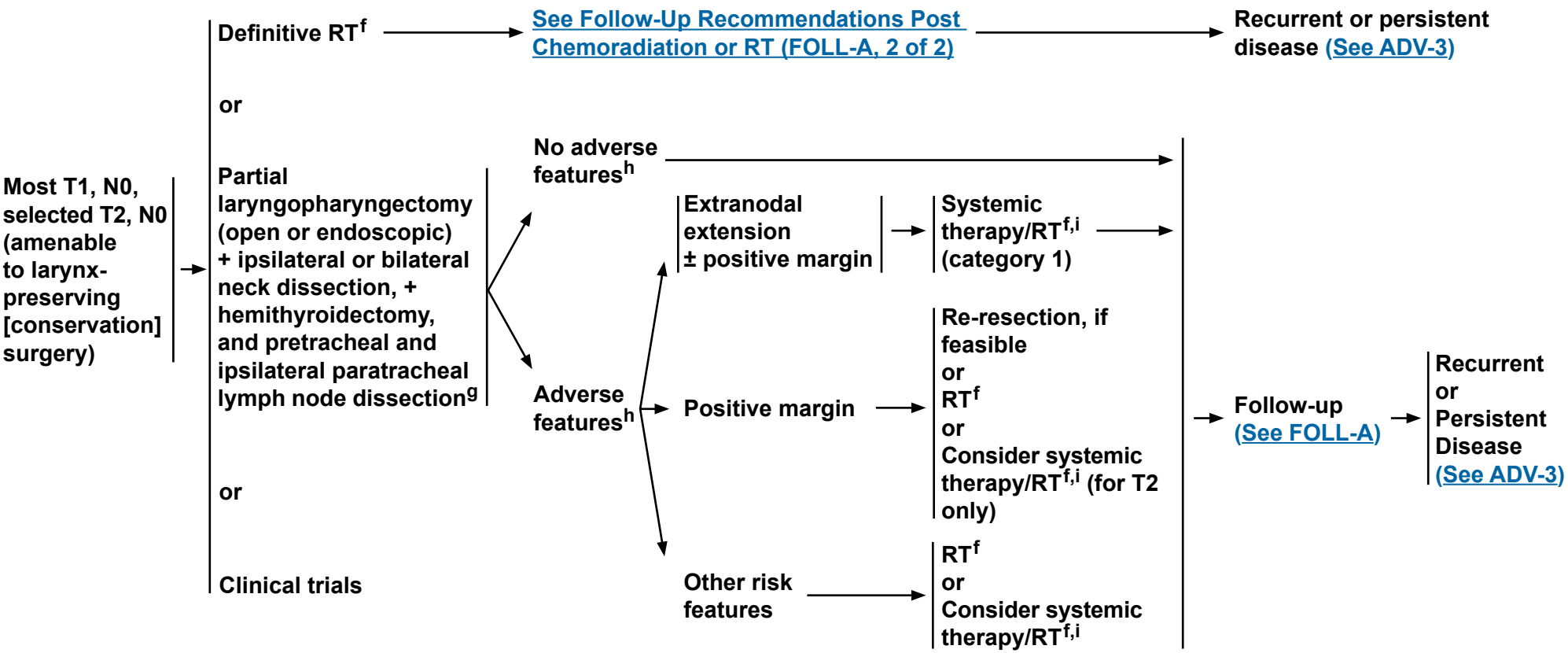

[f]See Principles of Radiation Therapy (HYPO-A).
[g]See Principles of Surgery (SURG-A).
[h]Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
[i]See Principles of Systemic Therapy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

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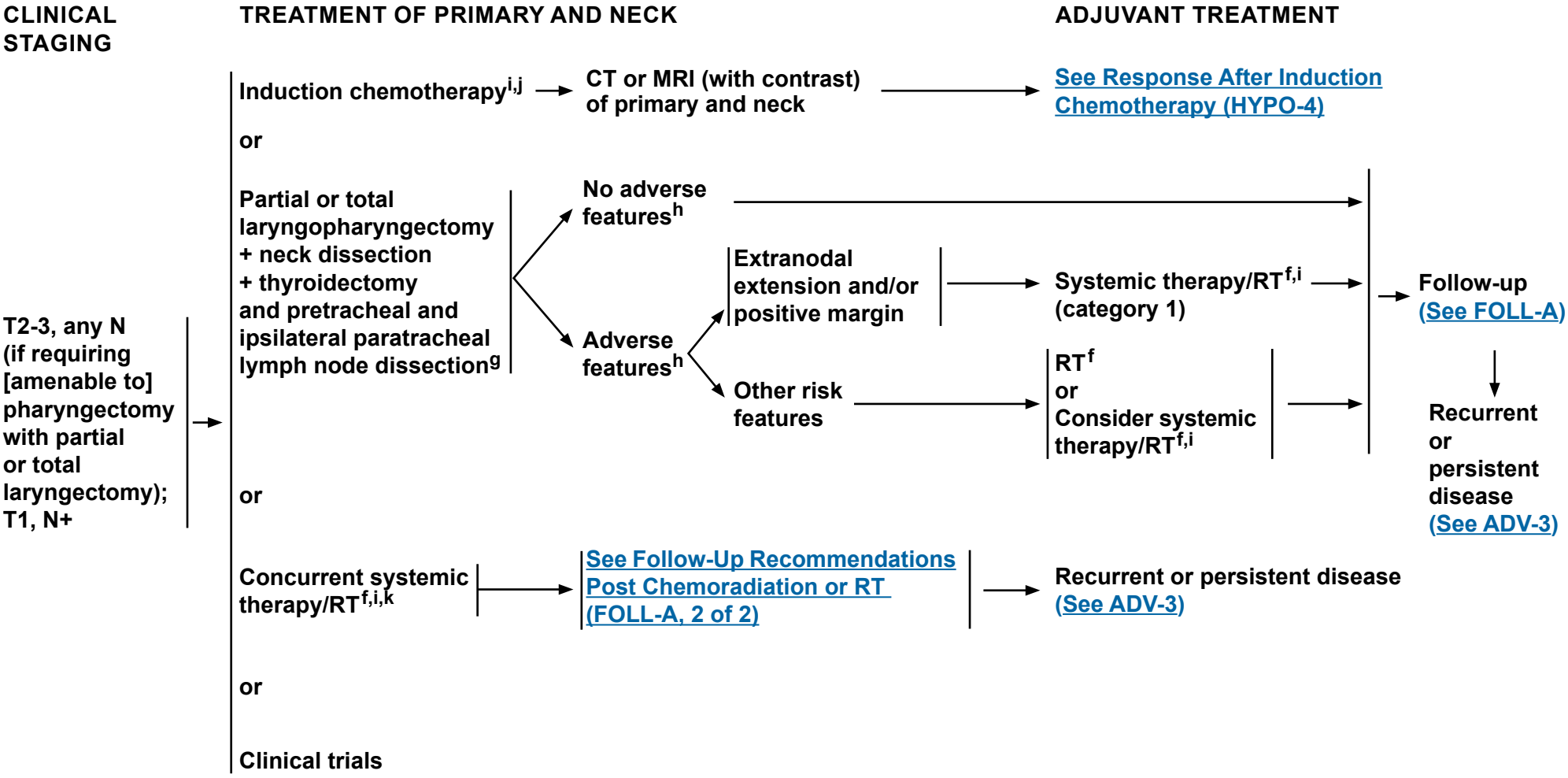

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[i] See Principles of Systemic Therapy (CHEM-A).
[j] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[k] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).

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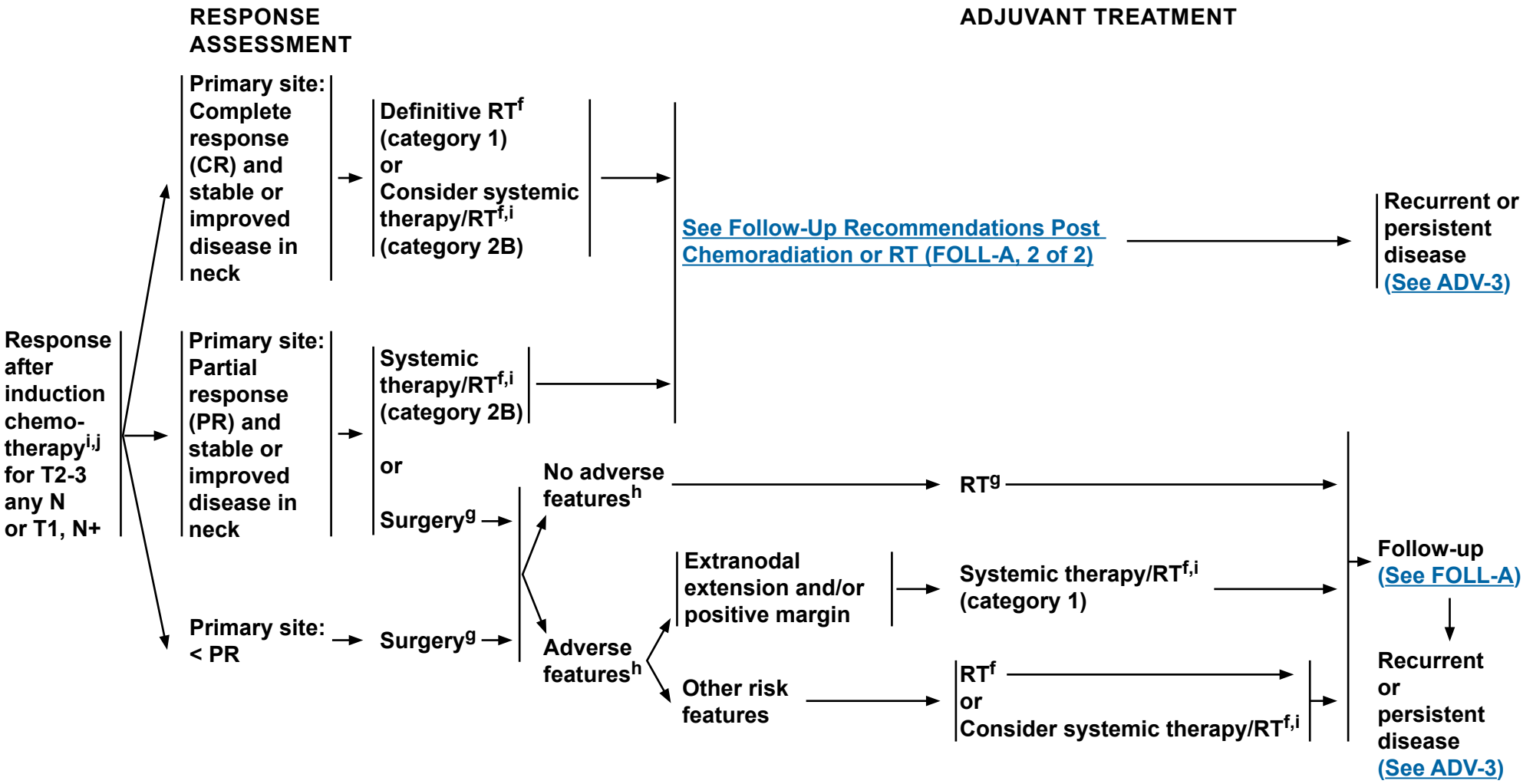

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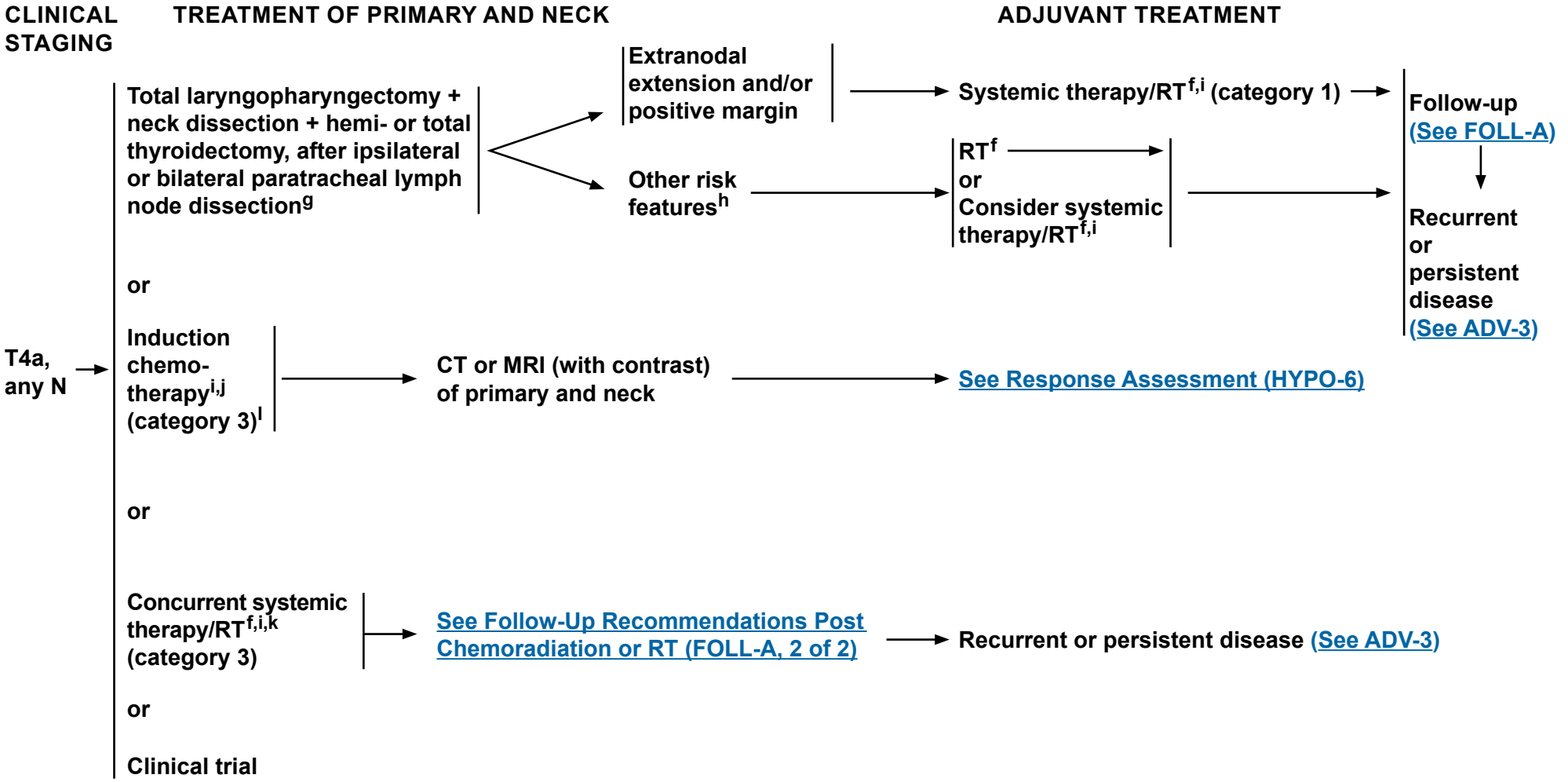

[f] See Principles of Radiation Therapy (HYPO-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
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[j] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
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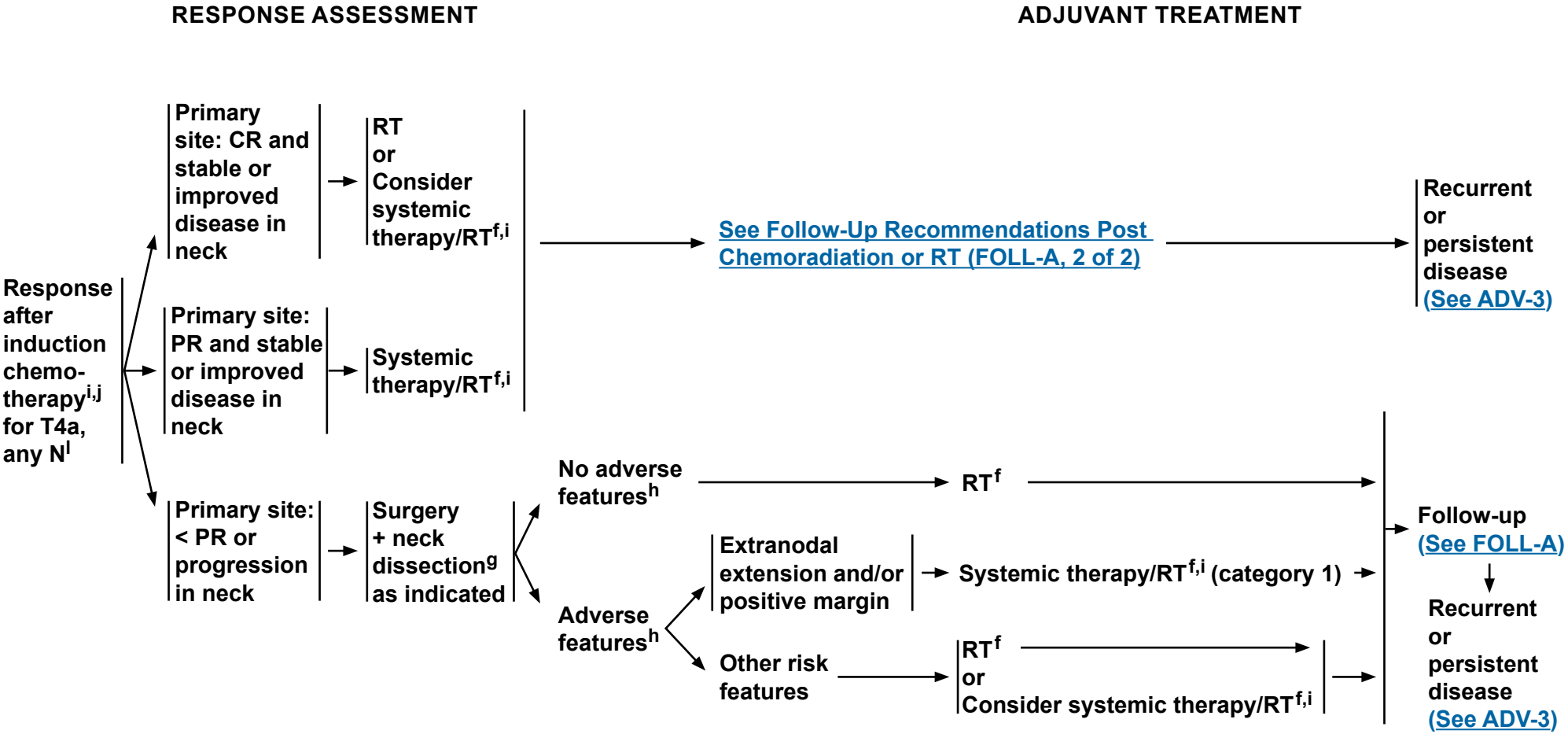

[f] See Principles of Radiation Therapy (HYPO-A).
[g] See Principles of Surgery (SURG-A).
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[j] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
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PRINCIPLES OF 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]**
      - **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)**
        - **66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **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 3D 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.

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Clinical Trials: NCCN believes that the best management of any patient with cancer 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 systemic therapy[6,8-11]**

Either IMRT or 3D 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).
[6]See Principles of Systemic Therapy (CHEM-A).

[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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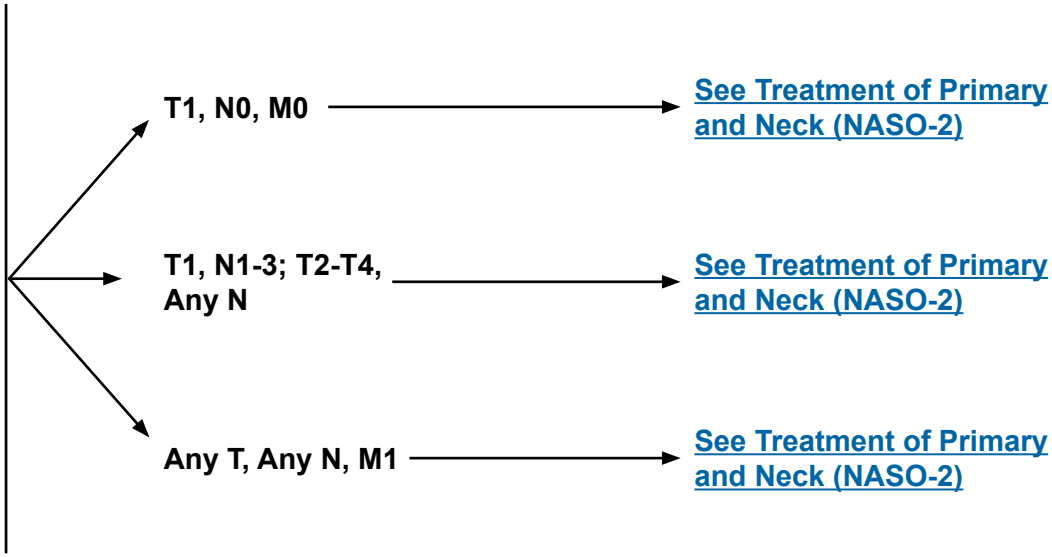
WORKUP

- **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 of skull base to clavicle ± CT of skull base/neck with contrast as clinically indicated to evaluate skull base erosion**
- **Dental,[c] nutritional, speech and swallowing, and audiology evaluations as clinically indicated[d]**
- **Imaging for distant metastases with FDG-PET/CT and/or chest CT with contrast**
- **Consider Epstein-Barr virus (EBV)/DNA testing[e]**
- **Consider ophthalmologic and endocrine evaluation as clinically indicated.**

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

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

[e]For nonkeratinizing or undifferentiated histology, consider testing for EBV in tumor and blood. Common means for detecting EBV in pathologic specimens include in situ hybridization for EBV-encoded RNA (EBER) or immunohistochemical staining for latent membrane protein (LMP). The EBV DNA load within the serum or plasma may be quantified using polymerase chain reaction (PCR) targeting genomic sequences of the EBV DNA such as BamHI-W, EBNA, or LMP; these tests vary in their sensitivity. The EBV DNA load may reflect prognosis and change in response to therapy.

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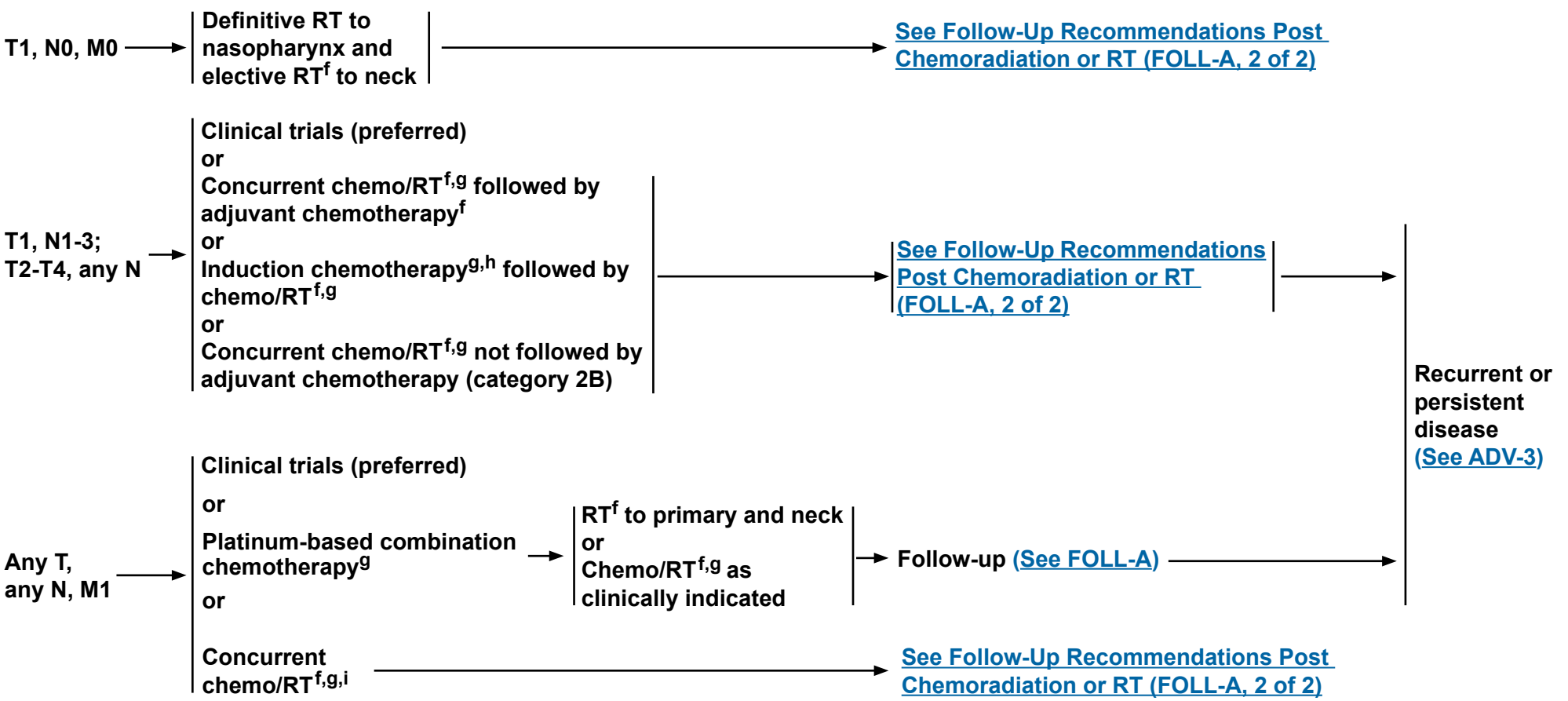

[f] See Principles of Radiation Therapy (NASO-A).
[g] See Principles of Systemic Therapy (CHEM-A).
[h] See Discussion on induction chemotherapy.
[i] Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any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

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone (for T1, N0 or patients who are not eligible to receive chemotherapy)

- **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]**

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the nasopharynx to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

[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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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Cancer of the Glottic Larynx

NCCN Guidelines Index
Table of Contents
Discussion

WORKUP[a]

- H&P[b,c] including a complete head and neck exam; mirror and/or fiberoptic examination as clinically indicated
- Biopsy of primary site or FNA of the neck
- Chest CT (with or without contrast) as clinically indicated[d]
- CT with contrast and thin angled 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[e]
- Nutrition, speech and swallowing evaluation/ therapy, and audiogram as clinically indicated[f]
- Consider videostrobe for select patients
- Pulmonary function evaluation for conservation surgery candidates

Multidisciplinary consultation as clinically indicated

CLINICAL STAGING / TREATMENT OF PRIMARY AND NECK

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 and biopsy are required. Direct laryngoscopy under anesthesia is generally recommended for all cases.

[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]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

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

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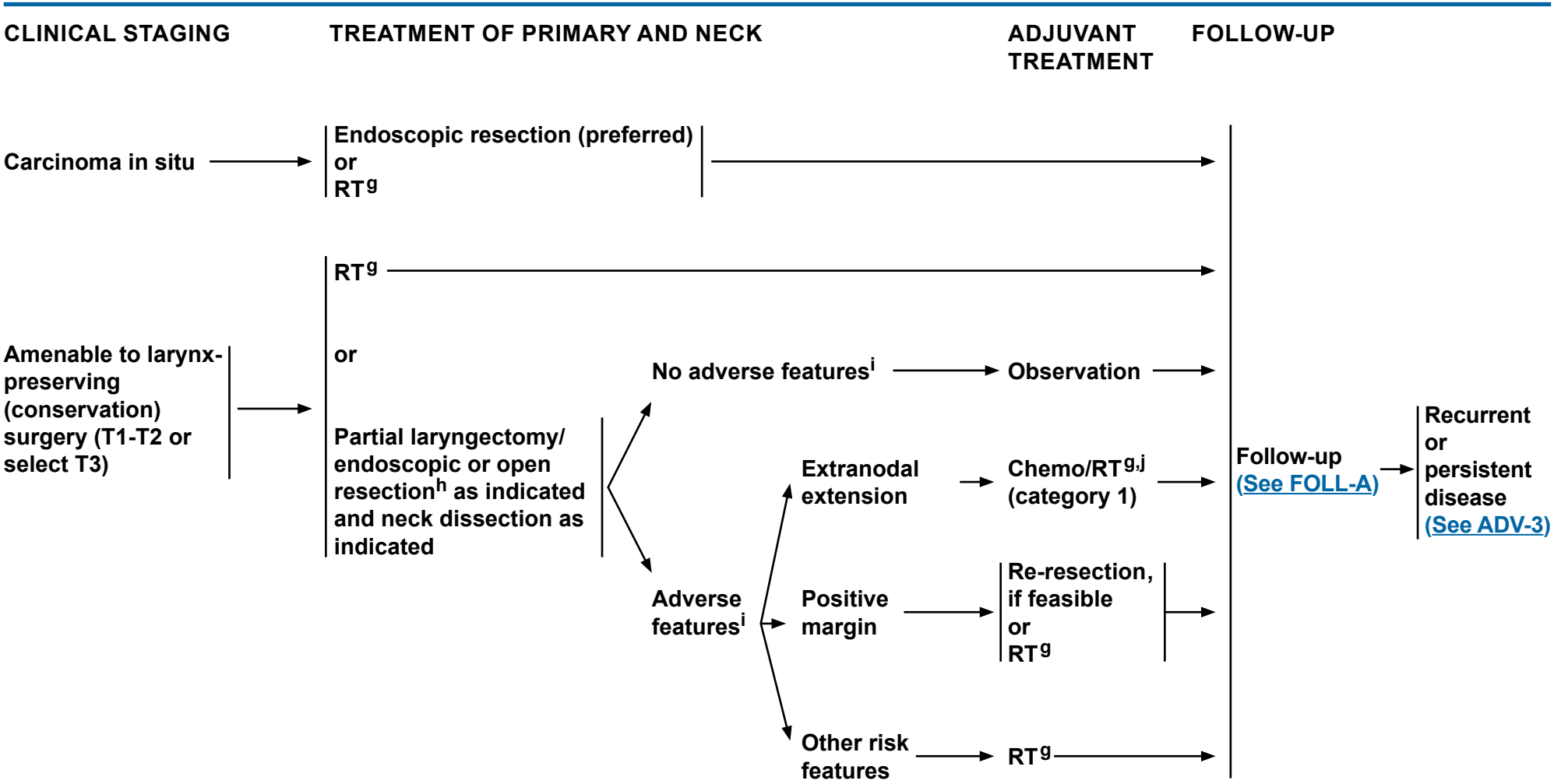

[g] See Principles of Radiation Therapy (GLOT-A).
[h] See Principles of Surgery (SURG-A).
[i] Adverse features: extranodal extension, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
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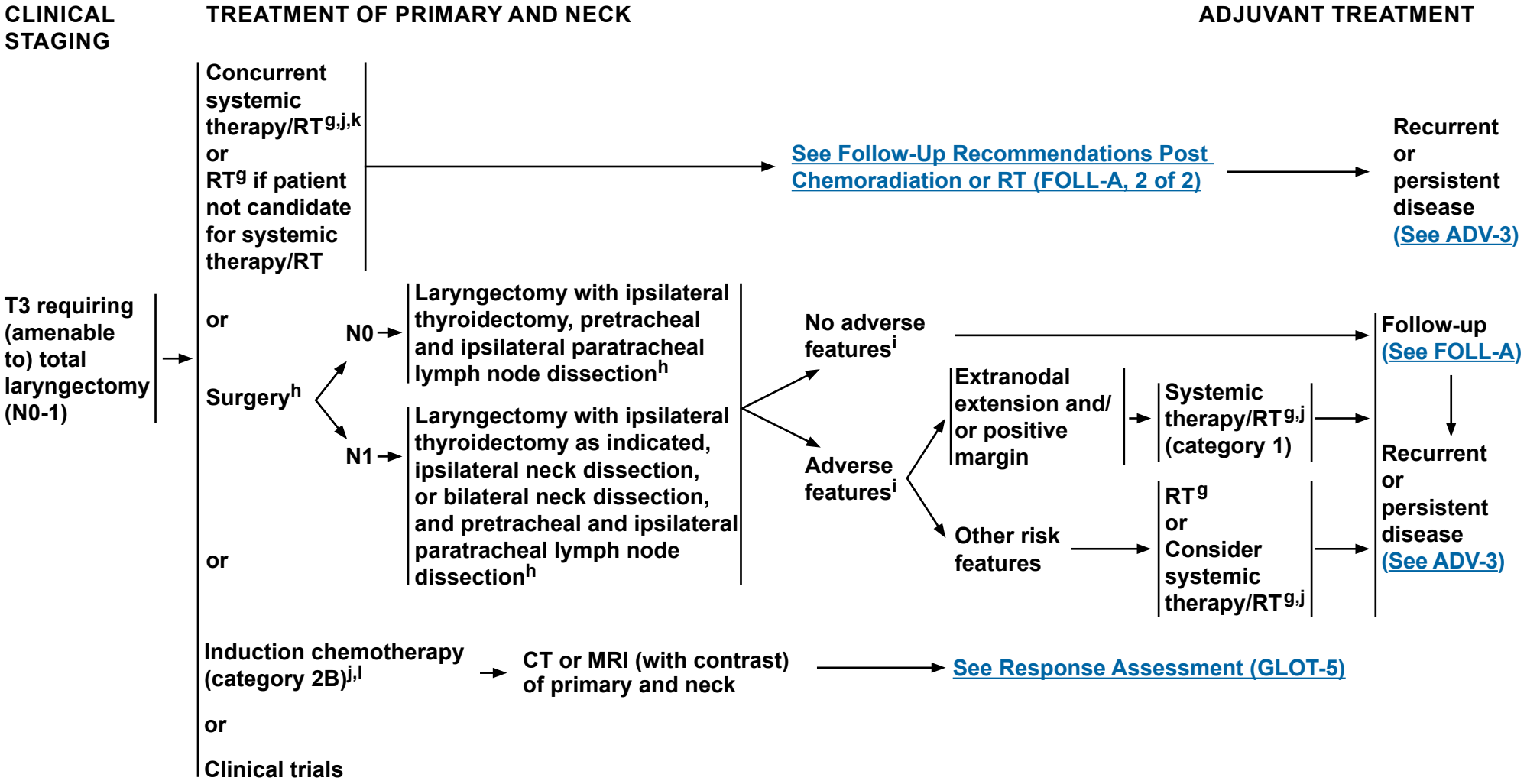

[g]See Principles of Radiation Therapy (GLOT-A).
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[i]Adverse features: extranodal extension, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
[j]See Principles of Systemic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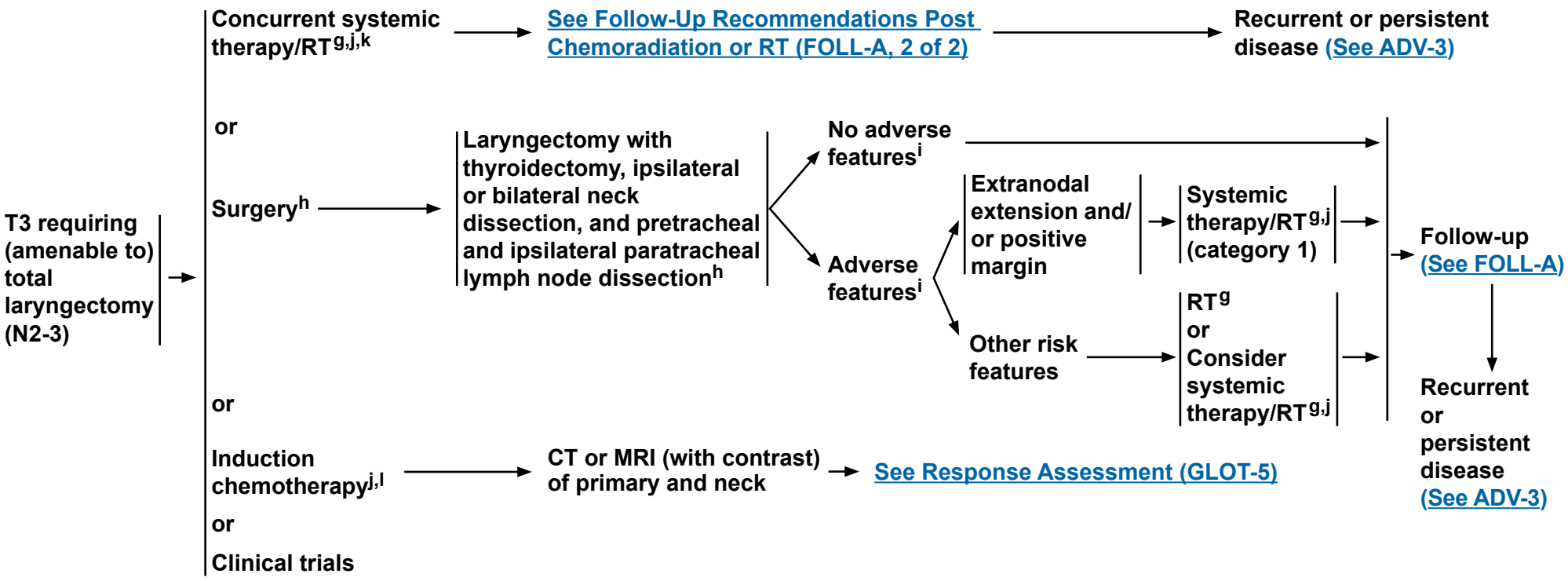

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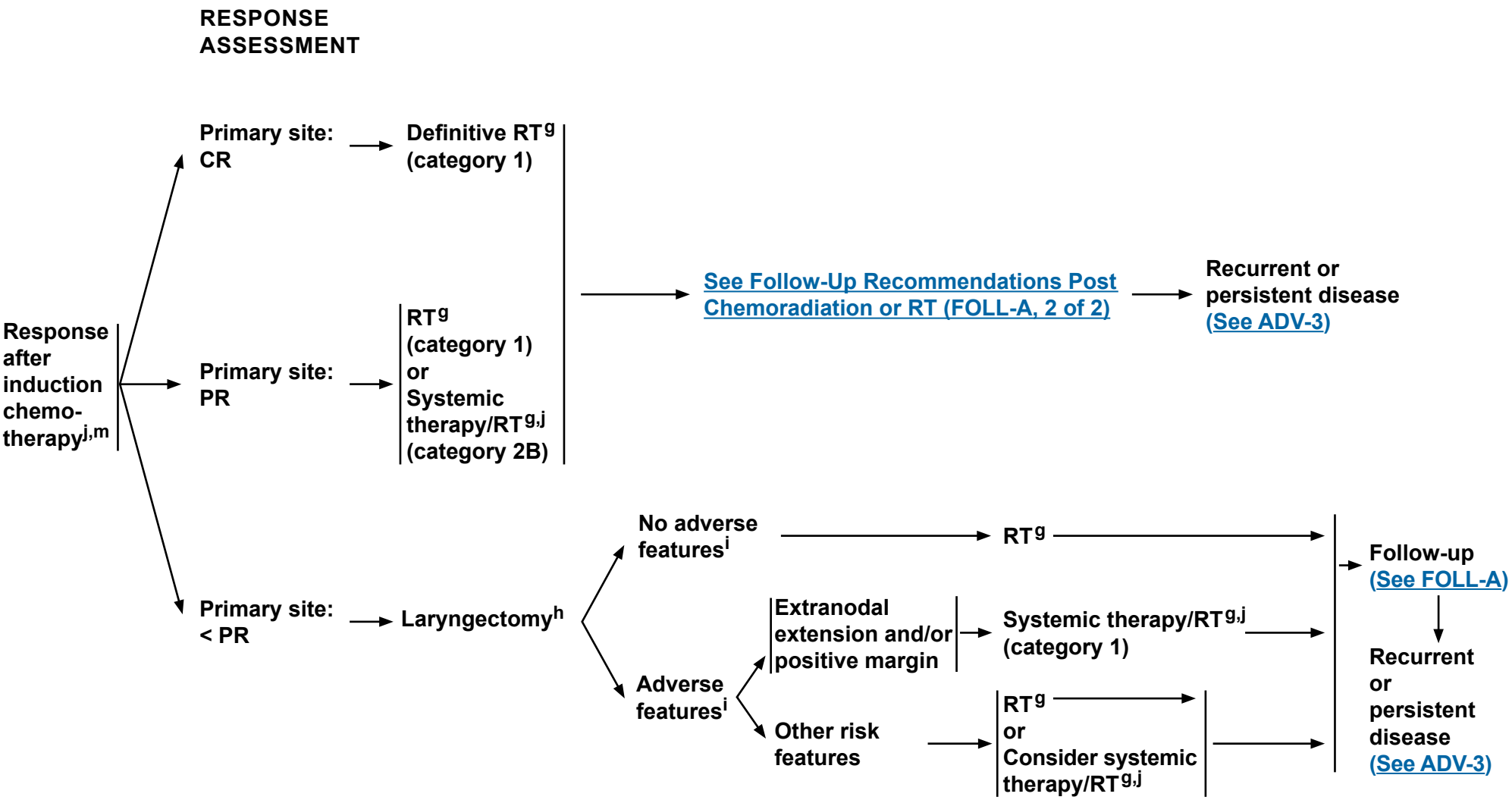

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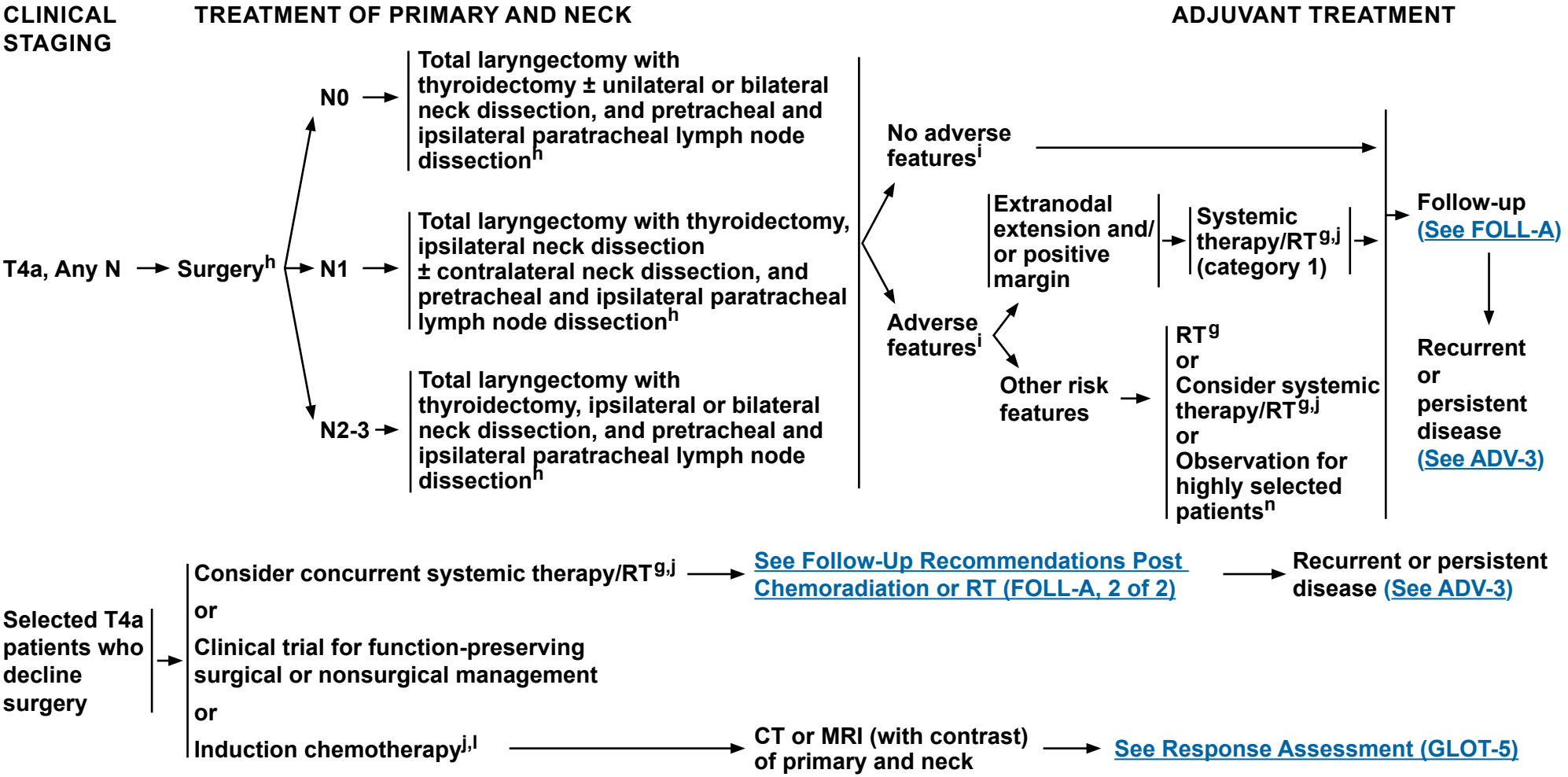

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[h]See Principles of Surgery (SURG-A).
[i]Adverse features: extranodal extension, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
[j]See Principles of Systemic Therapy (CHEM-A).
[l]See Discussion on induction chemotherapy.

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

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]**
      - **– 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)**
        - **▪ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **– 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 3D 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 patient with cancer 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 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 systemic therapy[4,6-9]**

Either IMRT or 3D 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).
[4]See Principles of Systemic Therapy (CHEM-A).

[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.
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NCCN Guidelines Version 2.2018
Cancer of the Supraglottic Larynx

NCCN Guidelines Index
Table of Contents
Discussion

WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and/or fiberoptic examination as clinically indicated
- Biopsy of primary site or FNA of the neck
- Chest CT (with or without contrast) as clinically indicated[c]
- CT with contrast and thin angled 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[d] as clinically indicated
- 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 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]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

[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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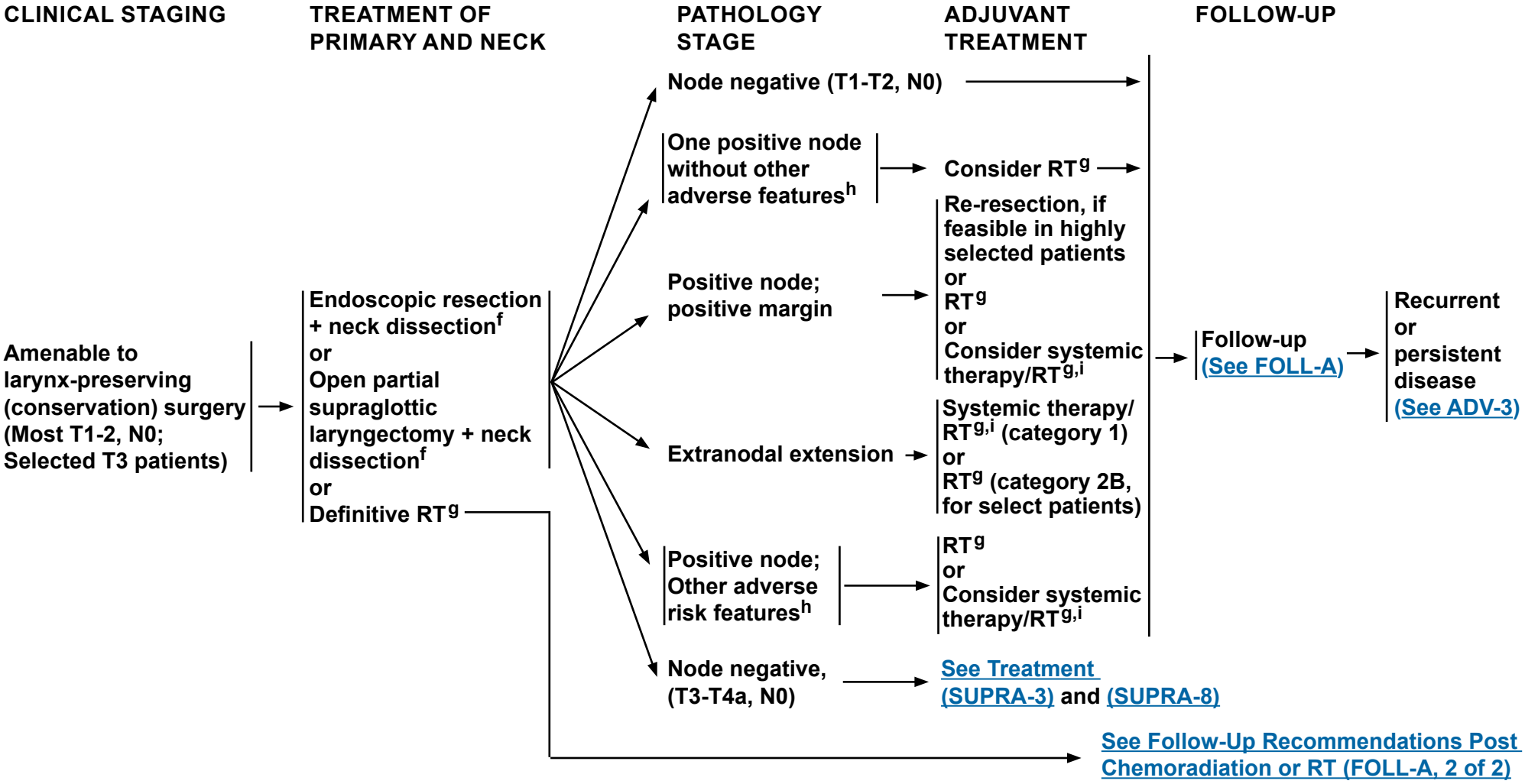

[f] See Principles of Surgery (SURG-A).
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[h] Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
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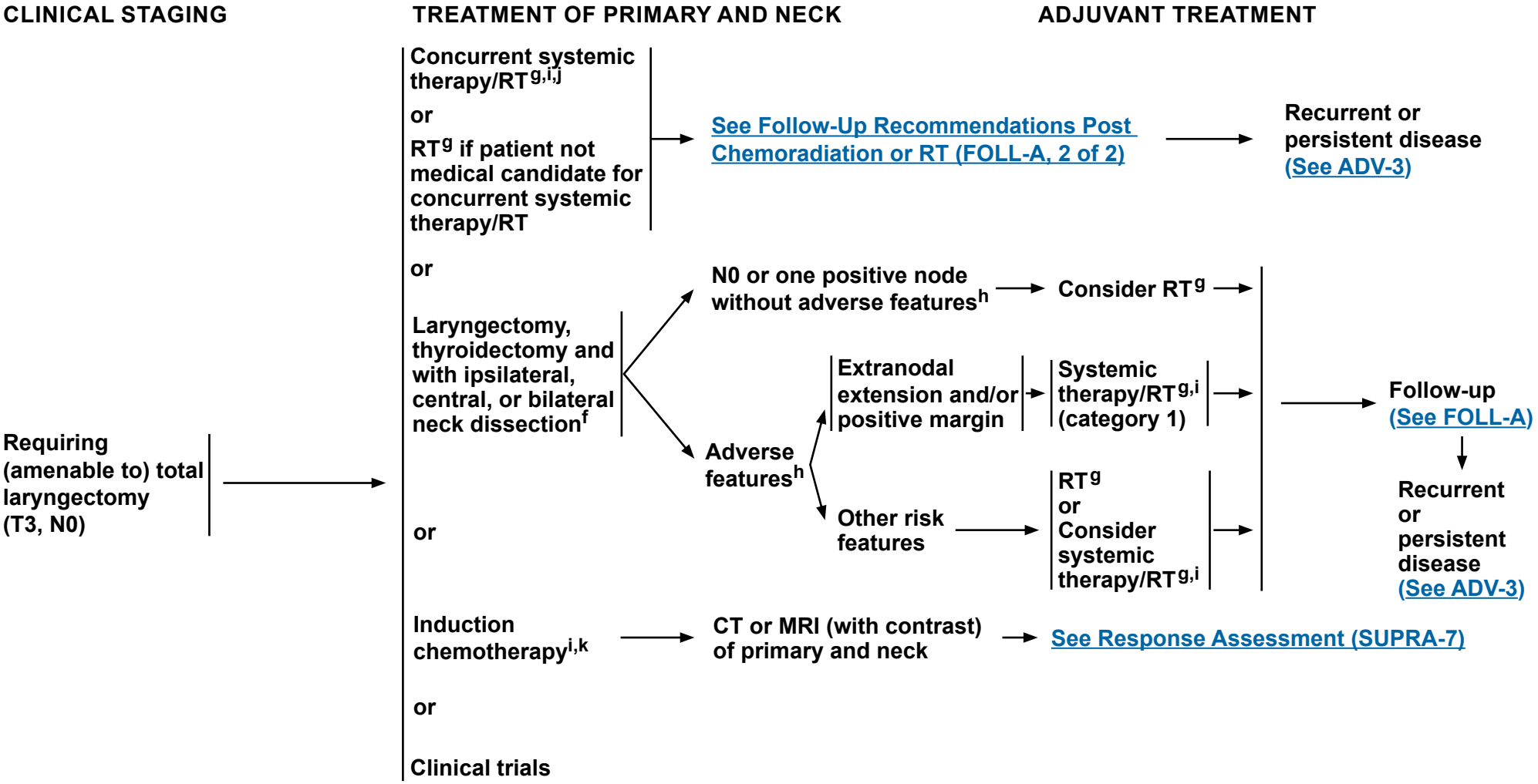

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CLINICAL STAGING

Node-positive disease

- **Amenable to larynx-preserving (conservation) surgery (T1-2, N+ and selected T3, N1)** → See Treatment of Primary and Neck (SUPRA-5)
- **Requiring (amenable to) total laryngectomy (Most T3, N2-3)** → See Treatment of Primary and Neck (SUPRA-6)
- **T4a, N1-N3** → See Treatment of Primary and Neck (SUPRA-8)
- **T4b, any N**
  or
  Unresectable nodal disease
  or
  Unfit for surgery → See Treatment of Head and Neck Cancer (ADV-1)

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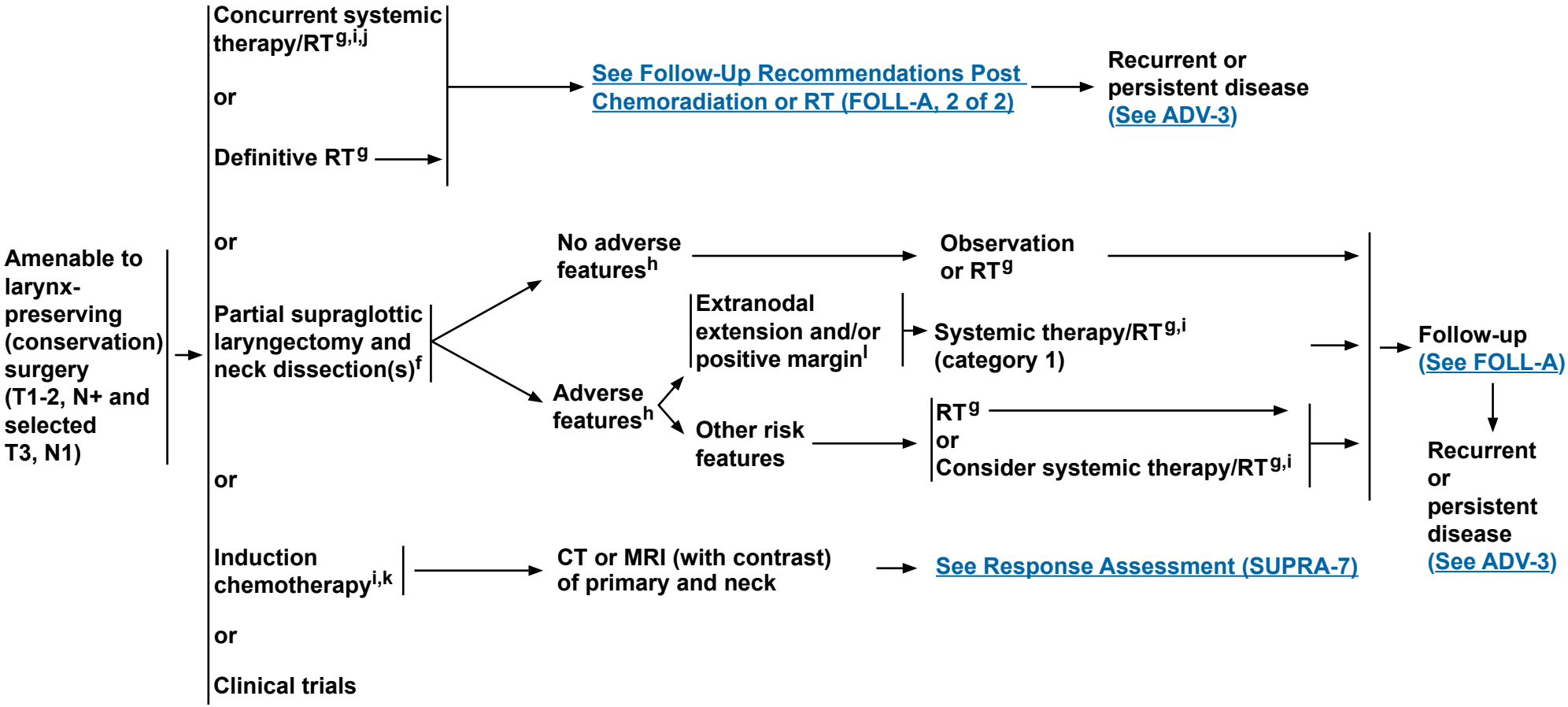

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[i]See Principles of Systemic Therapy (CHEM-A).
[j]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[k]See Discussion on induction chemotherapy.
[l]In highly select 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.

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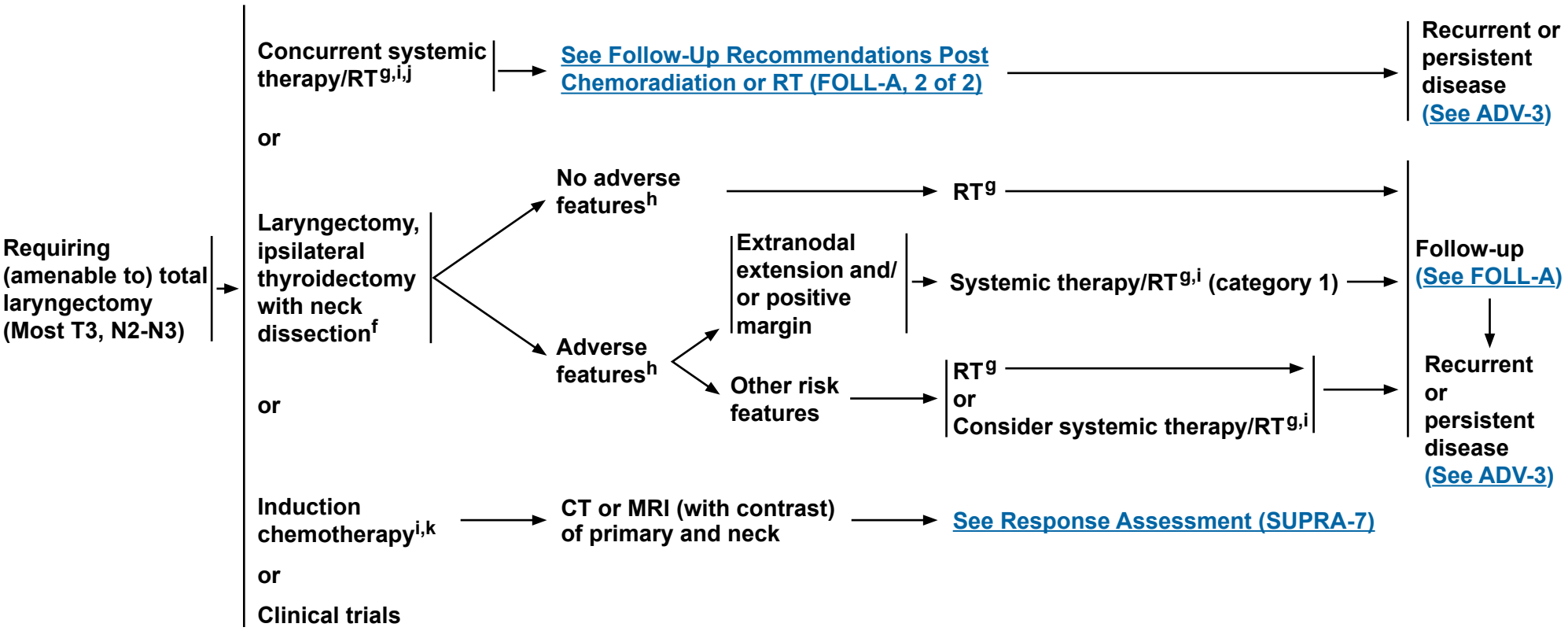

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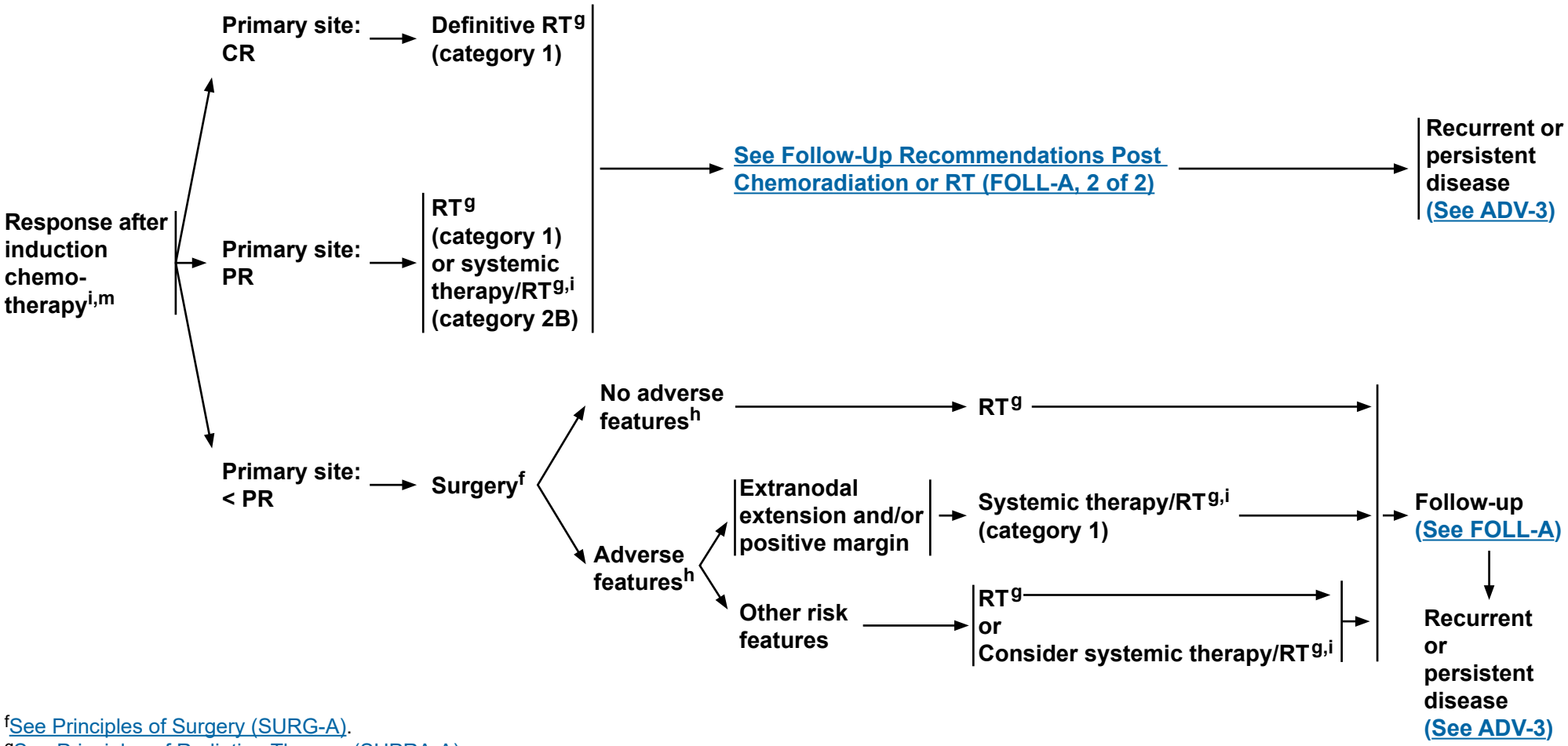
RESPONSE ASSESSMENT



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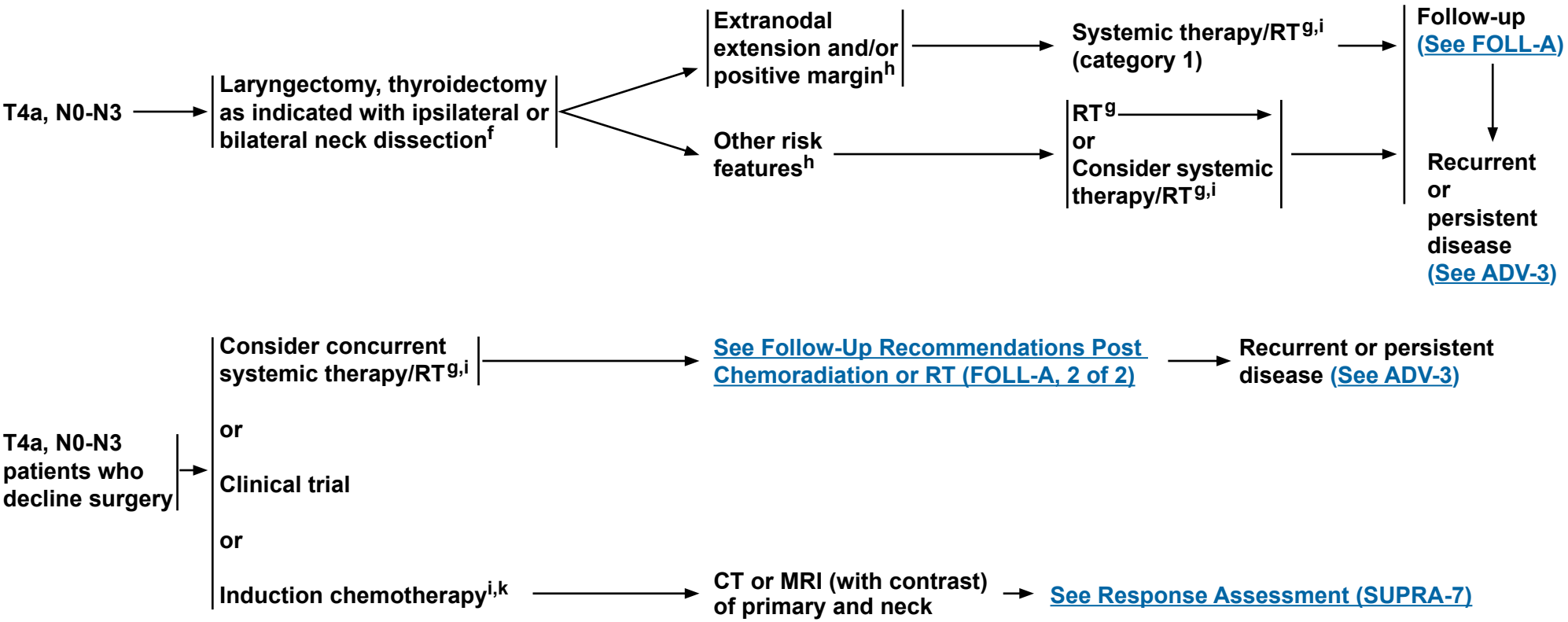

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PRINCIPLES OF RADIATION THERAPY[1]

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]**
      - **– 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)**
        - **66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **– 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 3D 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.

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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 h 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 systemic therapy[5,7-10]**

Either IMRT or 3D 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).

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

[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.

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

WORKUP

- H&P[a,b] including a complete head and neck exam; nasal endoscopy as clinically indicated
- CT with contrast or MRI with contrast of skull base
- Dental consultation[c] as clinically indicated
- Chest CT (with or without contrast) as clinically indicated[d]
- Consider FDG-PET/CT for stage III or IV

Multidisciplinary consultation as indicated

→ Biopsy

PATHOLOGY

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

→ 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]Chest CT is recommended for advanced nodal disease to screen for distant metastases.

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

[f]For SNUC, small cell, or SNEC histologies, systemic therapy should be a part of the overall treatment. Consider a clinical trial and referral to a major medical center that specializes in these diseases.

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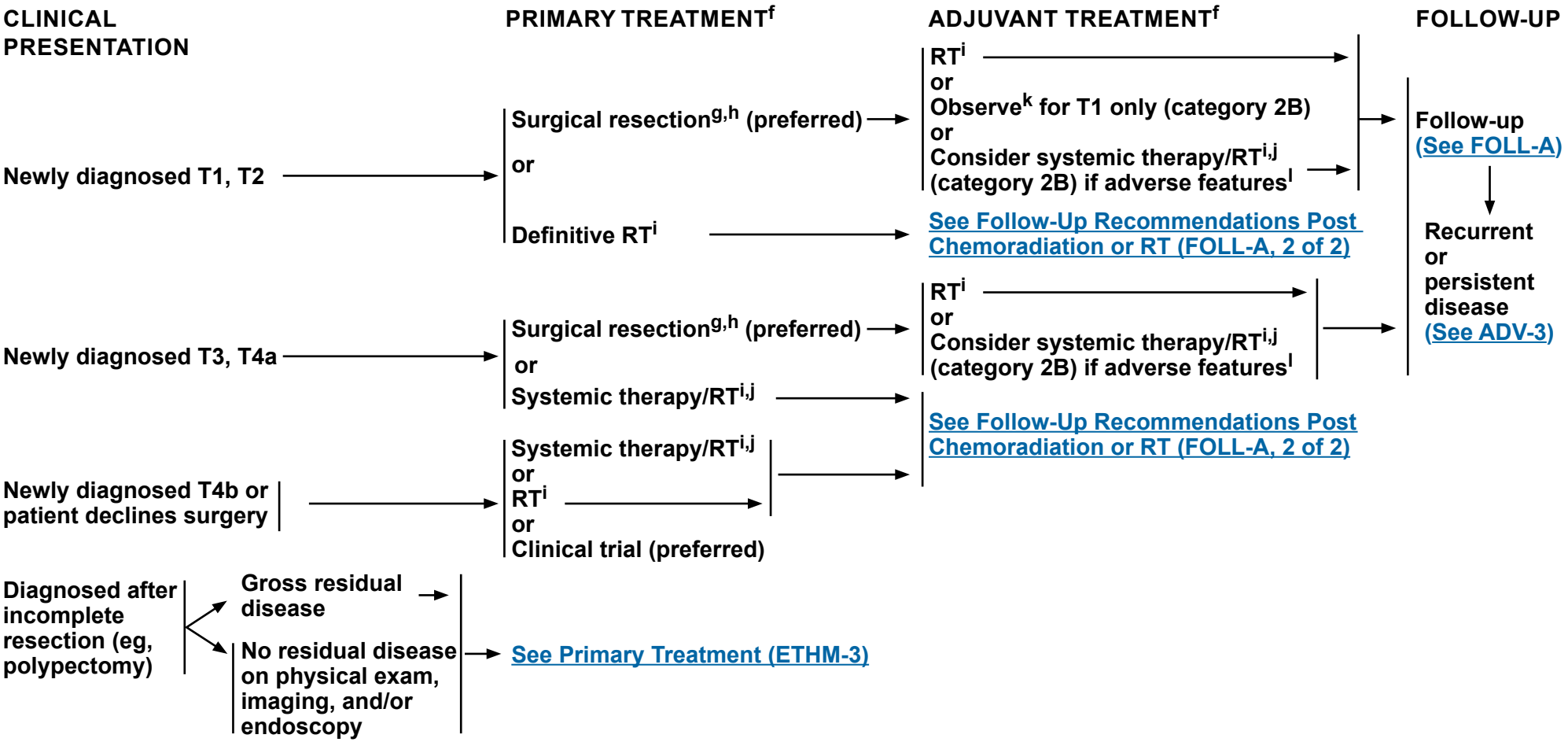


[f]For SNUC, small cell, or SNEC histologies, systemic therapy should be a part of the overall treatment. Consider a clinical trial and referral to a major medical center that specializes in these diseases.

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

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

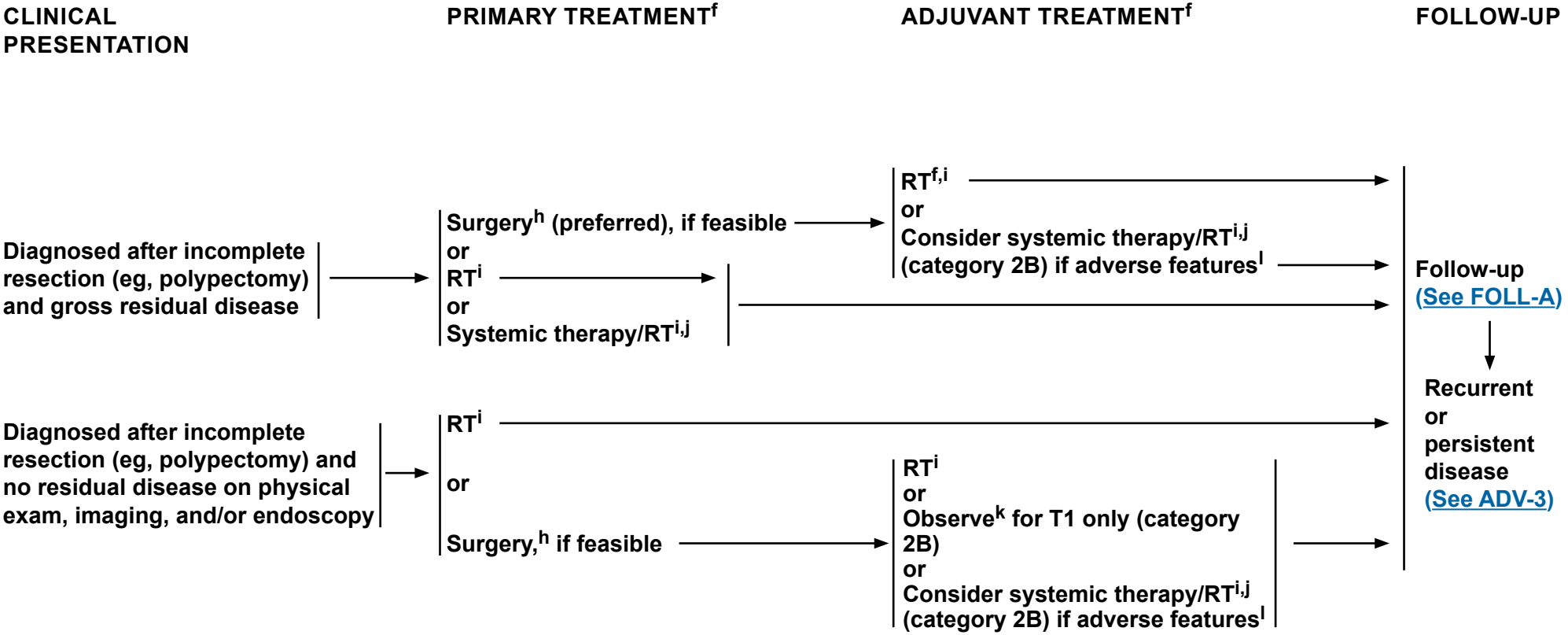
[i]See Principles of Radiation Therapy (ETHM-A). For minor salivary gland tumors, see SALI-A.

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

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

[l]Adverse features include positive margins, high-grade lesions, and intracranial extension (See Discussion).

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



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

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Clinical Trials: NCCN believes that the best management of any patient with cancer 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]
      - – 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)
        - ▪ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
      - – 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 l 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 systemic therapy[6]

Either IMRT(preferred) or 3D conformal RT is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

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

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WORKUP

- H&P[a,b] including a complete head and neck exam; nasal endoscopy as clinically indicated
- Complete head and neck CT with contrast and/or MRI with contrast
- Dental[c]/prosthetic consultation as clinically indicated
- Chest CT (with or without contrast) as clinically indicated[d]
- Consider FDG-PET/CT for Stage III or IV

Multidisciplinary consultation as indicated

→ **Biopsy[e]**

PATHOLOGY

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

→ **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).

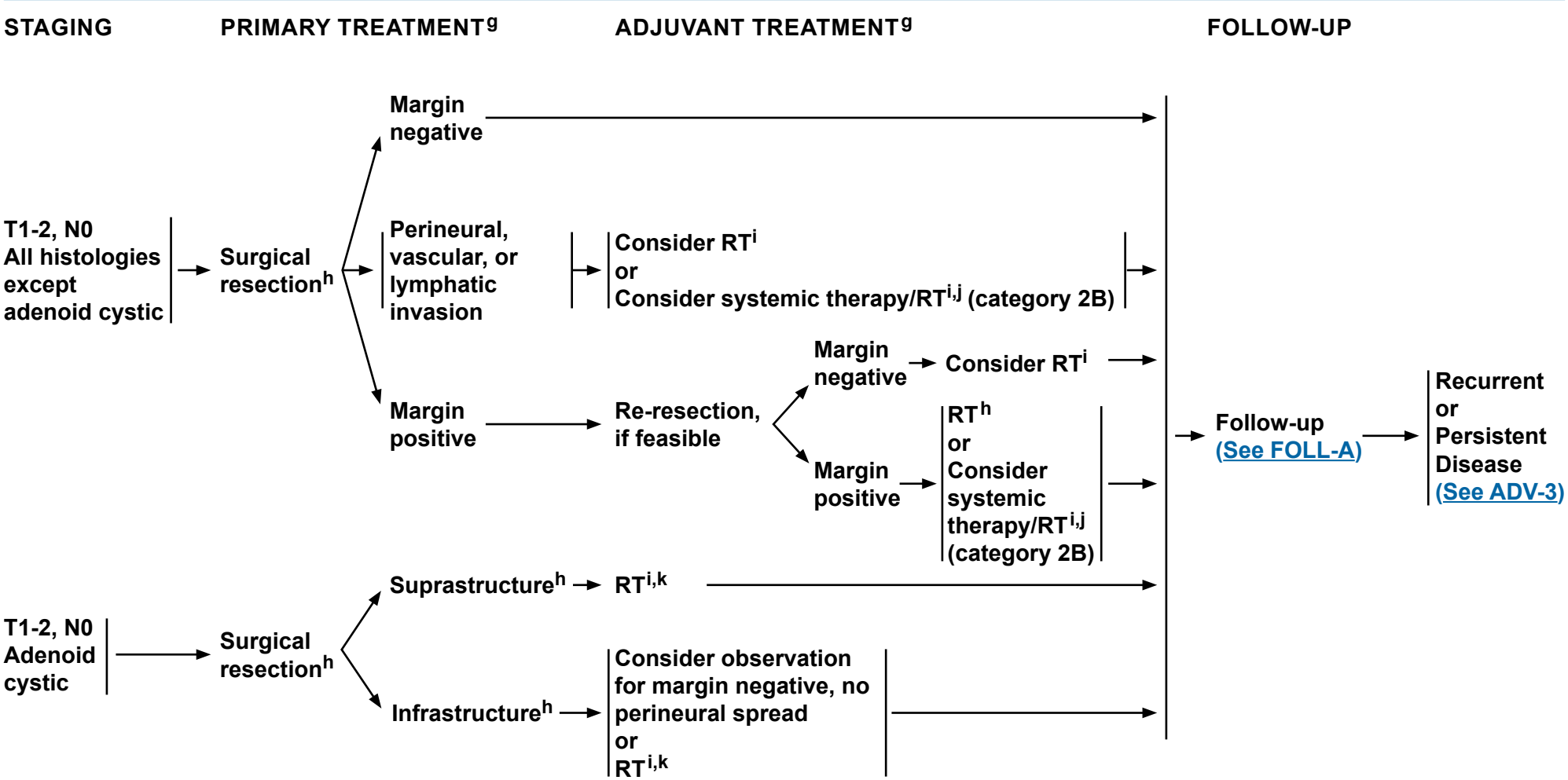
[d]Chest CT is recommended for advanced nodal disease to screen for distant metastases.

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

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

[g]For SNUC, small cell, or SNEC histologies, systemic therapy should be a part of the overall treatment. Consider a clinical trial and 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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

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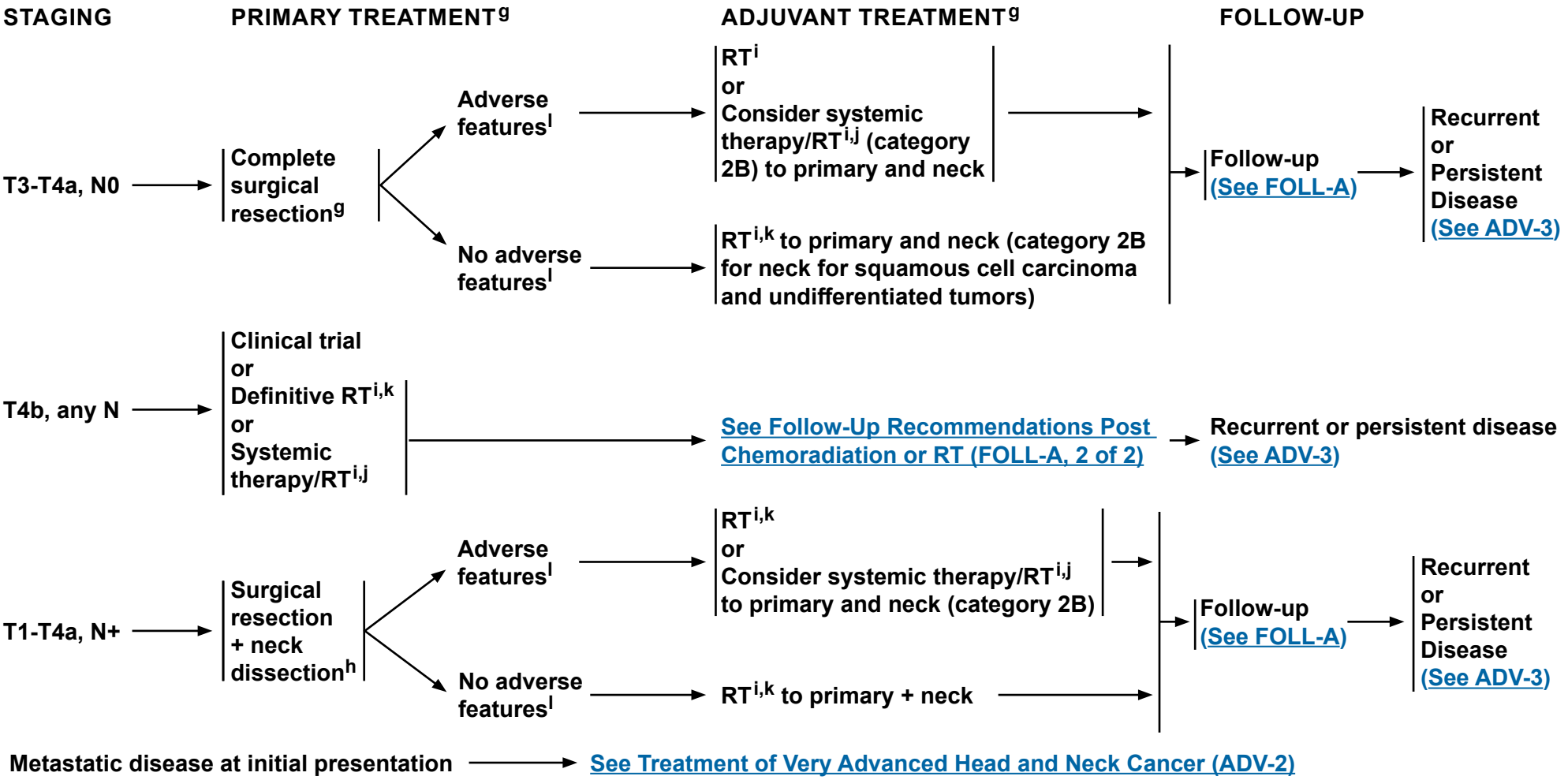

[g]For SNUC, small cell, or SNEC histologies, systemic therapy should be a part of the overall treatment. Consider a clinical trial and referral to a major medical center that specializes in these diseases.
[h]See Principles of Surgery (SURG-A).
[i]See Principles of Radiation Therapy (MAXI-A).
[j]See Principles of Systemic Therapy (CHEM-A).
[k]For adenoid cystic tumors and minor salivary gland tumors, see SALI-A.
[l]Adverse features include positive margins or extranodal extension (See Discussion).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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]
      - – 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)
        - ▪ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
      - – 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 l 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 systemic therapy[6]

Either IMRT (preferred) or 3D conformal RT is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

[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).

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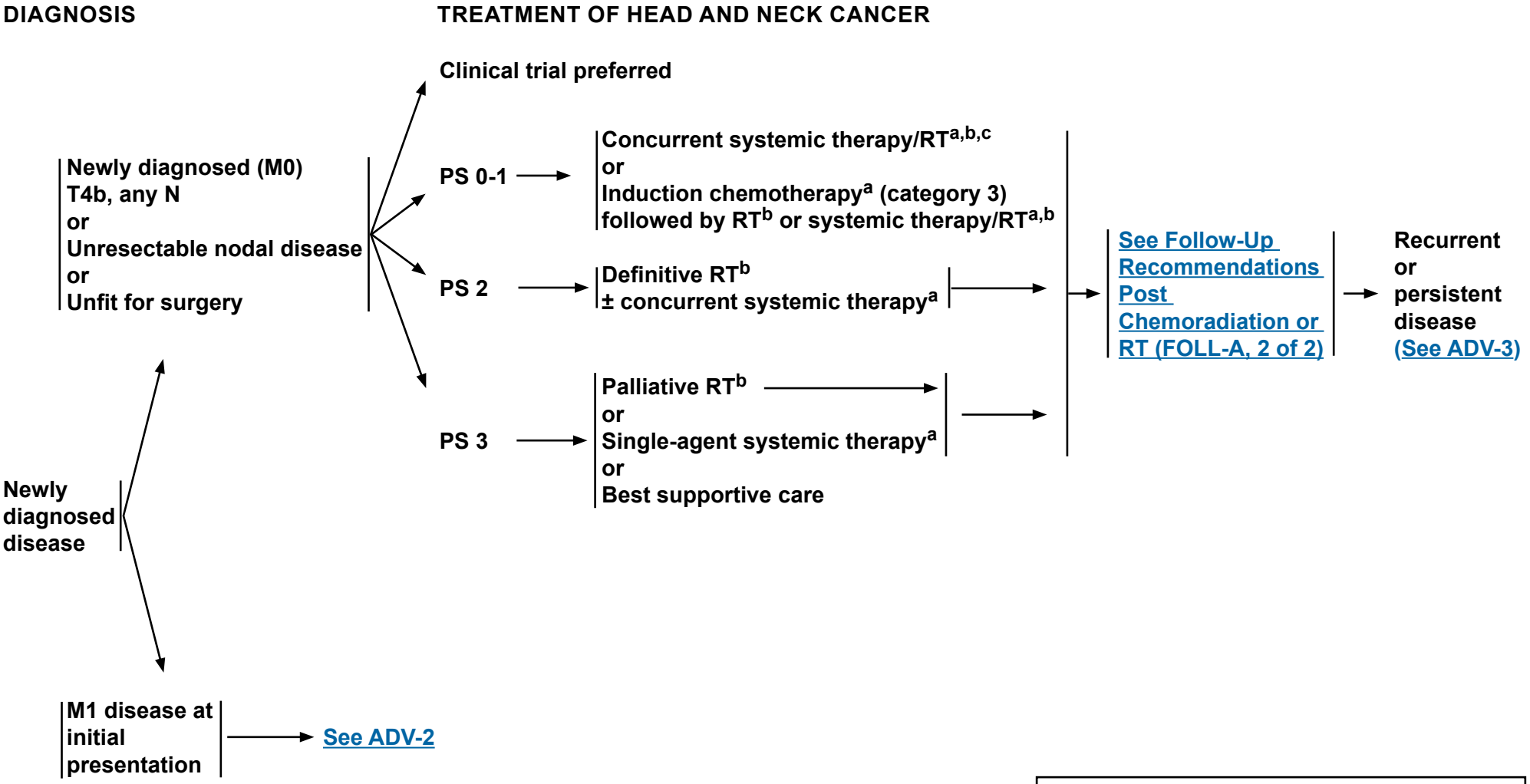

[a] See Principles of Systemic Therapy (CHEM-A).
[b] See Principles of Radiation Therapy (ADV-A).
[c] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).

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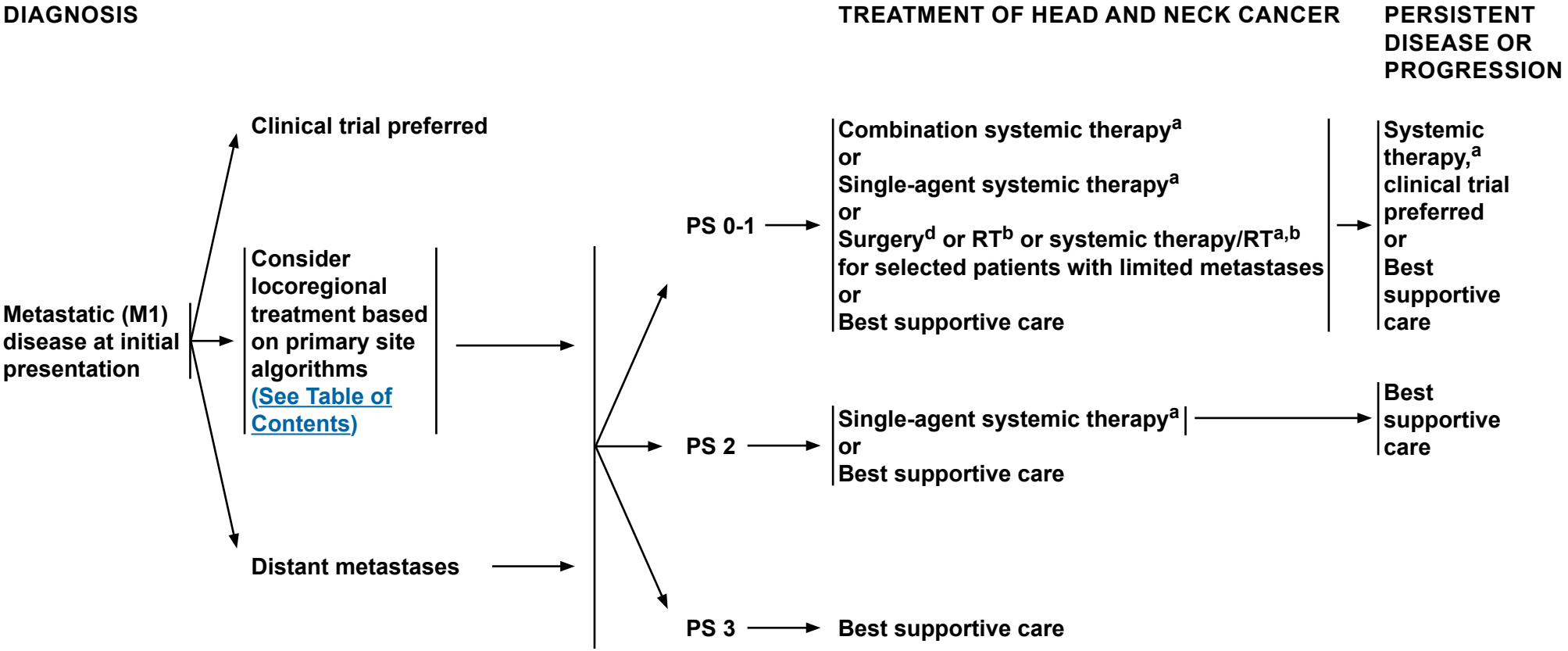

[a] See Principles of Systemic Therapy (CHEM-A).
[b] See Principles of Radiation Therapy (ADV-A).
[d] See Principles of Surgery (SURG-A).

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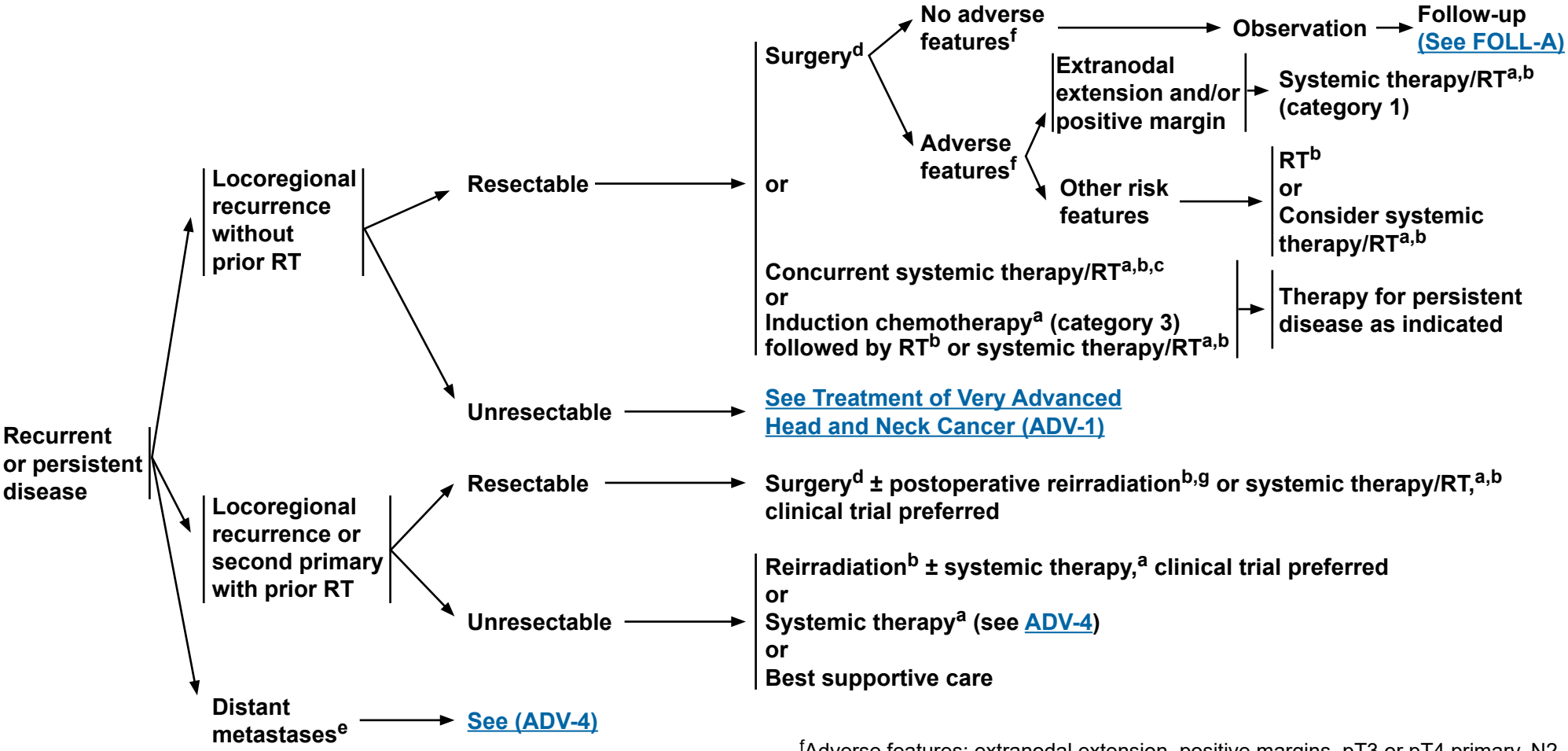
DIAGNOSIS

TREATMENT OF HEAD AND NECK CANCER



[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).
[e] Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).
[f] Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic 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).

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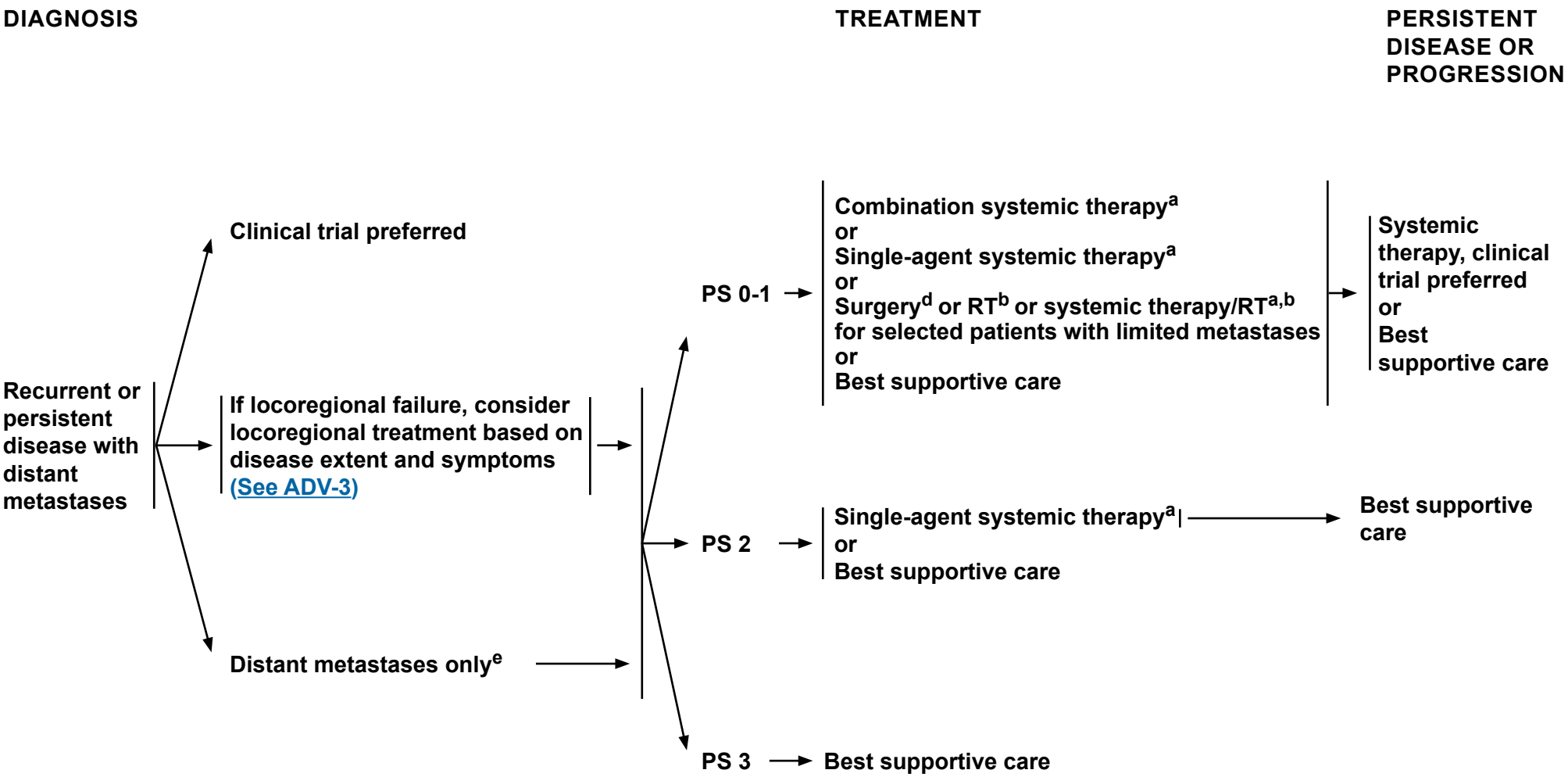

[a]See Principles of Systemic Therapy (CHEM-A).
[b]See Principles of Radiation Therapy (ADV-A).
[d]See Principles of Surgery (SURG-A).
[e]Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).

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

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] Data indicate that accelerated fractionation does not offer improved efficacy over conventional fractionation.[6,7] 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 described in 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. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)

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

[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] 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.

[6] Ang K, Zhang Q, Wheeler RH, et al. A phase III trial (RTOG 0129) of two radiation-cisplatin regimens for head and neck carcinomas (HNC): Impact of radiation and cisplatin intensity on outcome [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 5507.

[7] 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.

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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[8]**
      - **– 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)**
        - **66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **– 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 3D 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 systemic therapy[3,9-11]**

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

[2] In general, the reirradiated population of head and neck cancer patients described in 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. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)

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

[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).

[8] 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.

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

[10] 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.

[11] 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.

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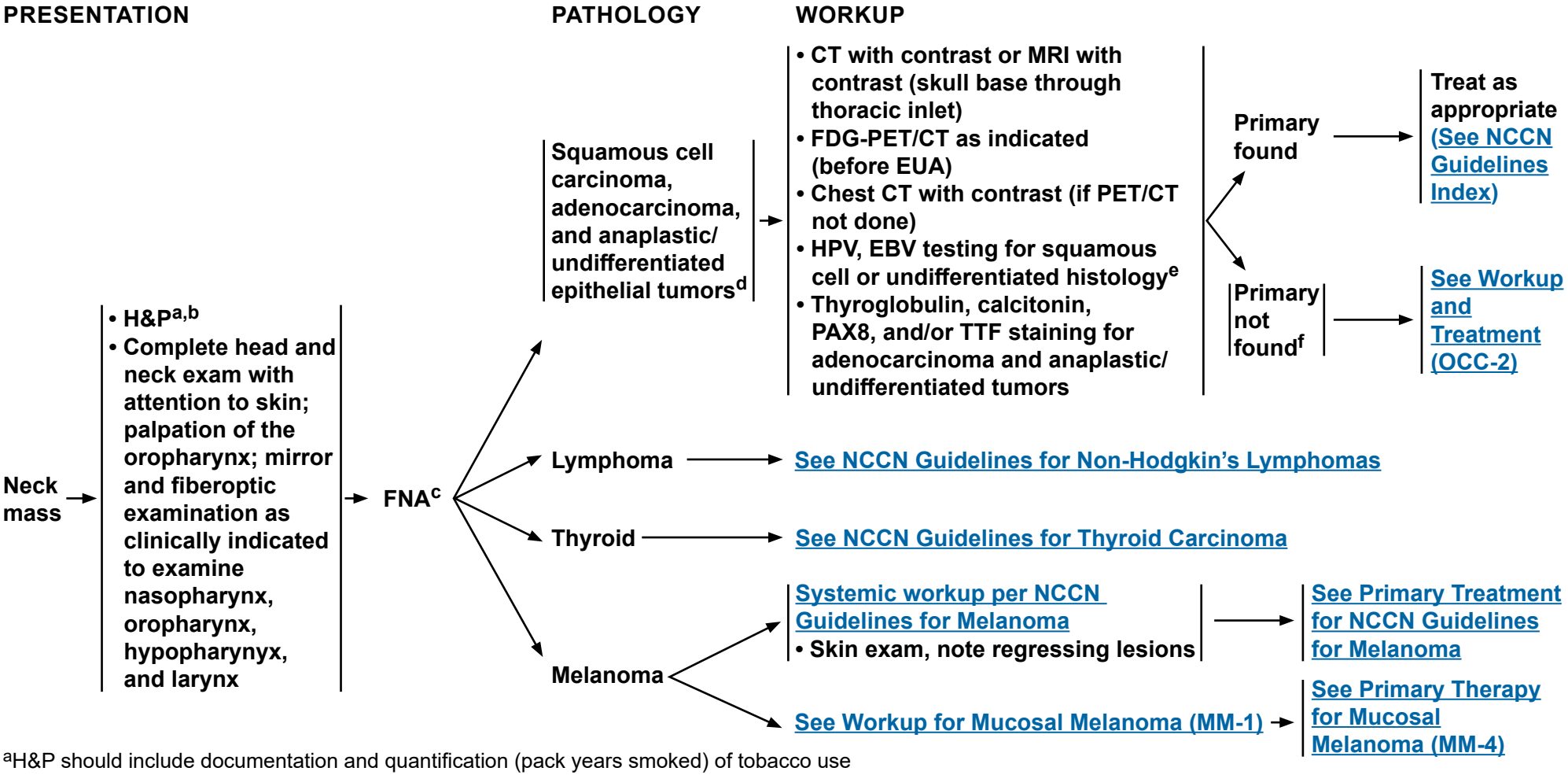

[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation 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.

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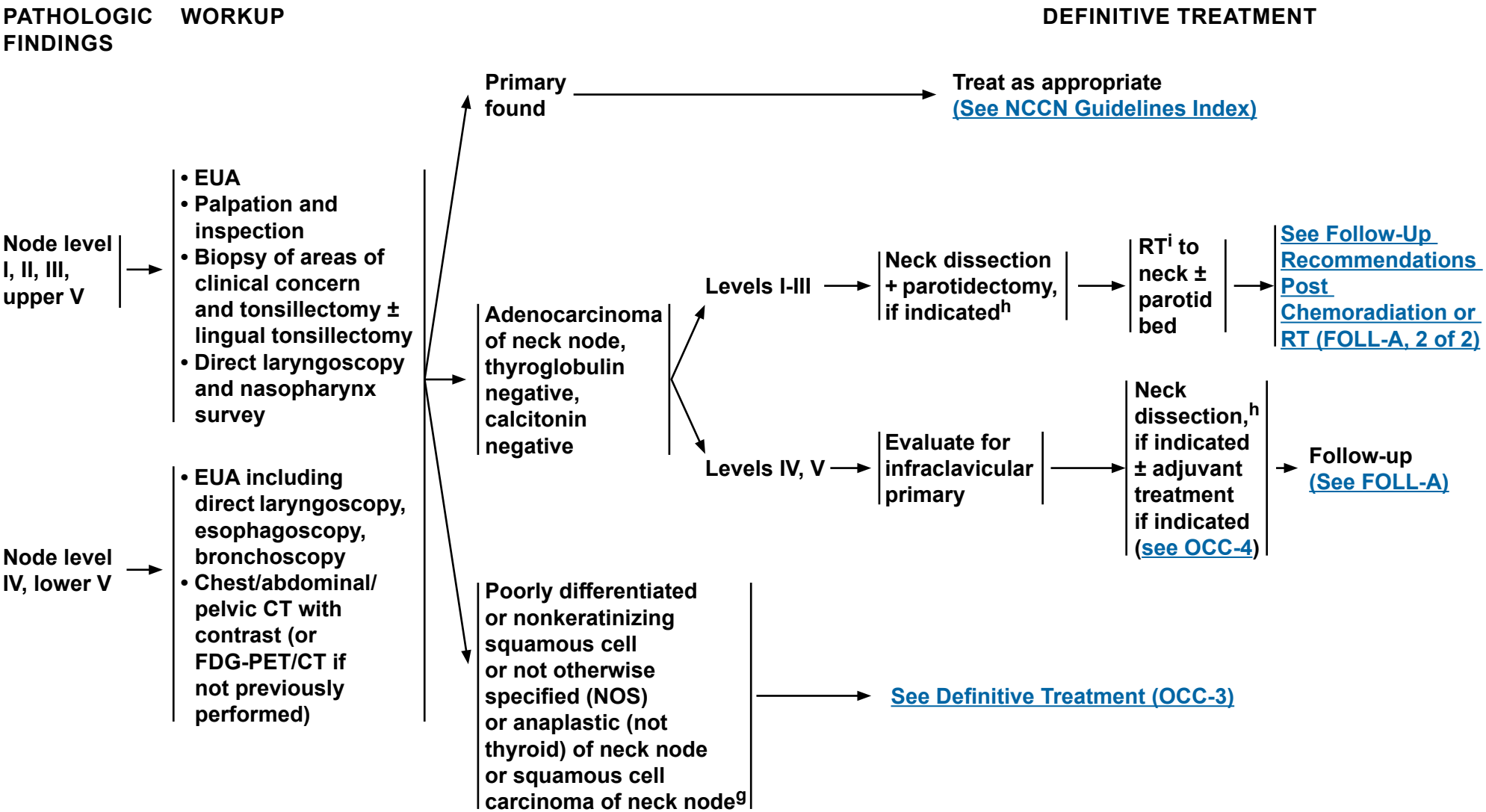

[g]HPV and EBV testing are suggested if not yet done.
[h]See Principles of Surgery (SURG-A).
[i]See Principles of Radiation Therapy (OCC-A).

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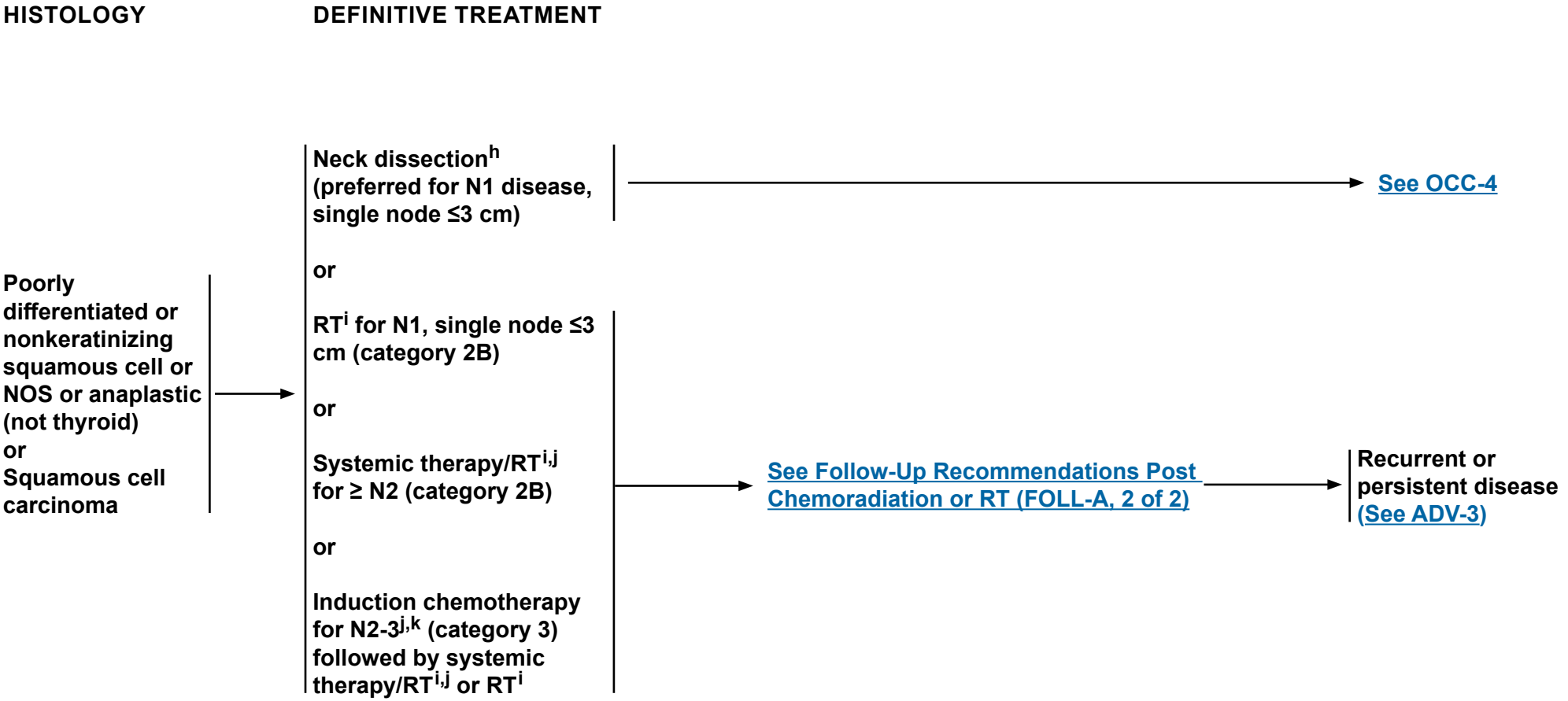

[h] See Principles of Surgery (SURG-A).
[i] See Principles of Radiation Therapy (OCC-A).
[j] See Principles of Systemic Therapy (CHEM-A).
[k] See Discussion on induction chemotherapy.

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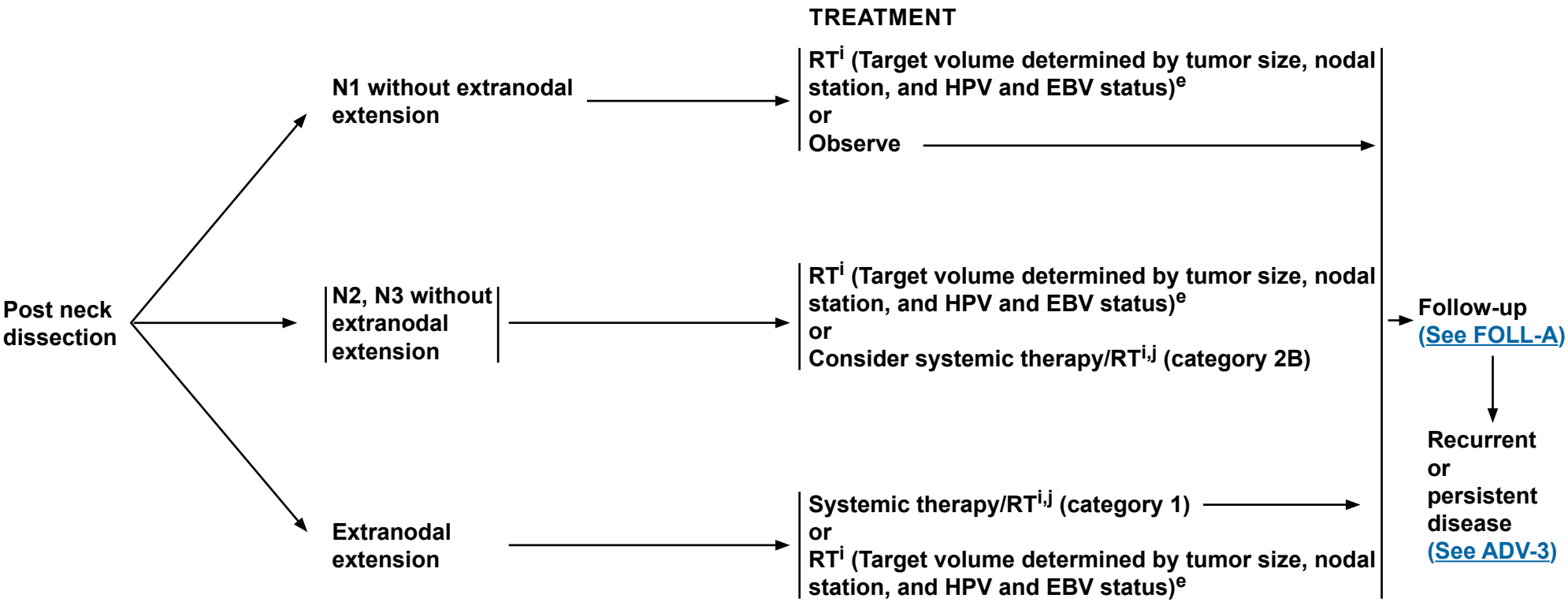

[e]Whether HPV or EBV positive status may help to define the radiation fields is being investigated (See Principles of Surgery [SURG-A 2 of 8] and Discussion).
[i]See Principles of Radiation Therapy (OCC-A).
[j]See Principles of Systemic Therapy (CHEM-A).

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

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 3D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures.

[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 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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 extranodal extension (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 systemic therapy[5,7-10]**

Either IMRT or 3D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures.

[1]For squamous cell carcinoma, adenocarcinoma, and poorly differentiated carcinoma.
[2]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).
[5]See Principles of Systemic Therapy (CHEM-A).

[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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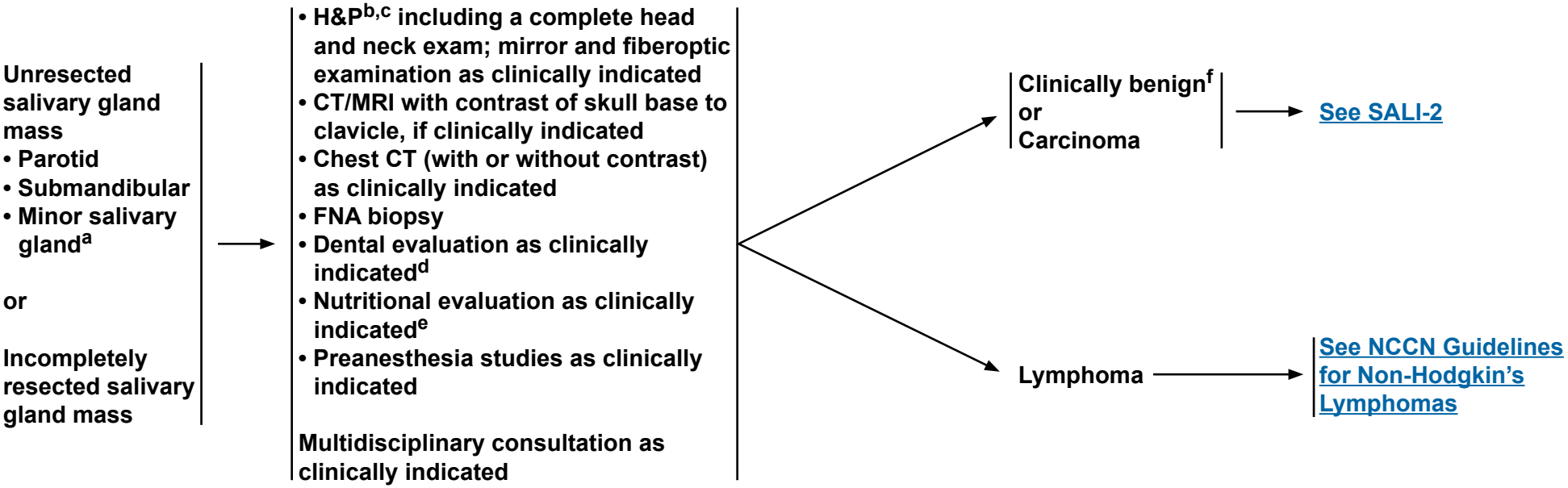
CLINICAL PRESENTATION

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]See Principles of Dental Evaluation and Management (DENT-A).
[e]See Principles of Nutrition: Management and Supportive Care (NUTR-A).
[f]Characteristics of a benign tumor include mobile superficial lobe, slow growth, painless, V and/or VII intact, and no neck nodes.

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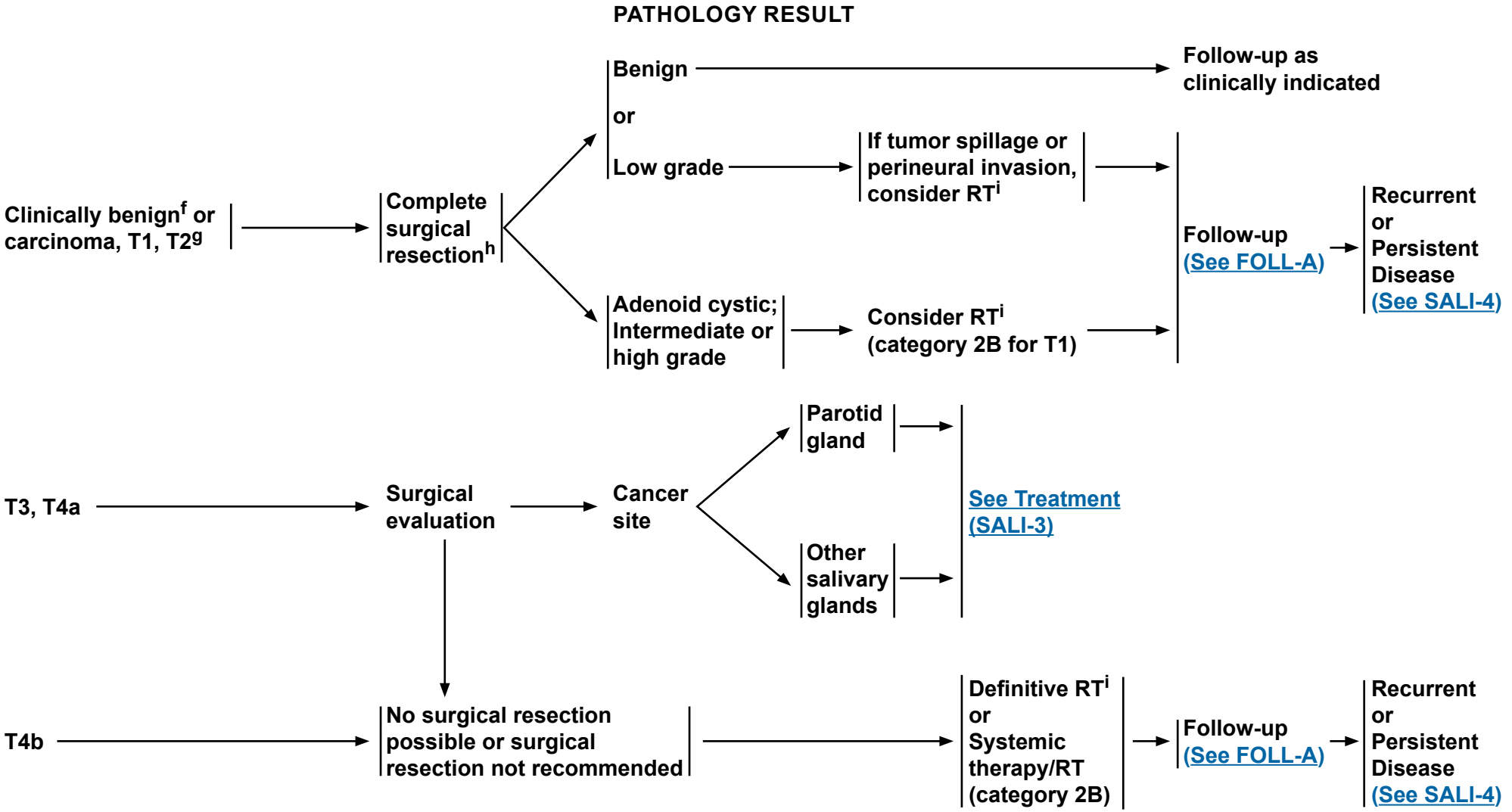

[f]Characteristics of a benign tumor include mobile superficial lobe, slow growth, no pain, VII intact, and no neck nodes.
[g]If incidental N+ disease is present go to SALI-3.
[h]Surgical resection of a clinically benign tumor includes: no enucleation of lateral lobe and intraoperative communication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

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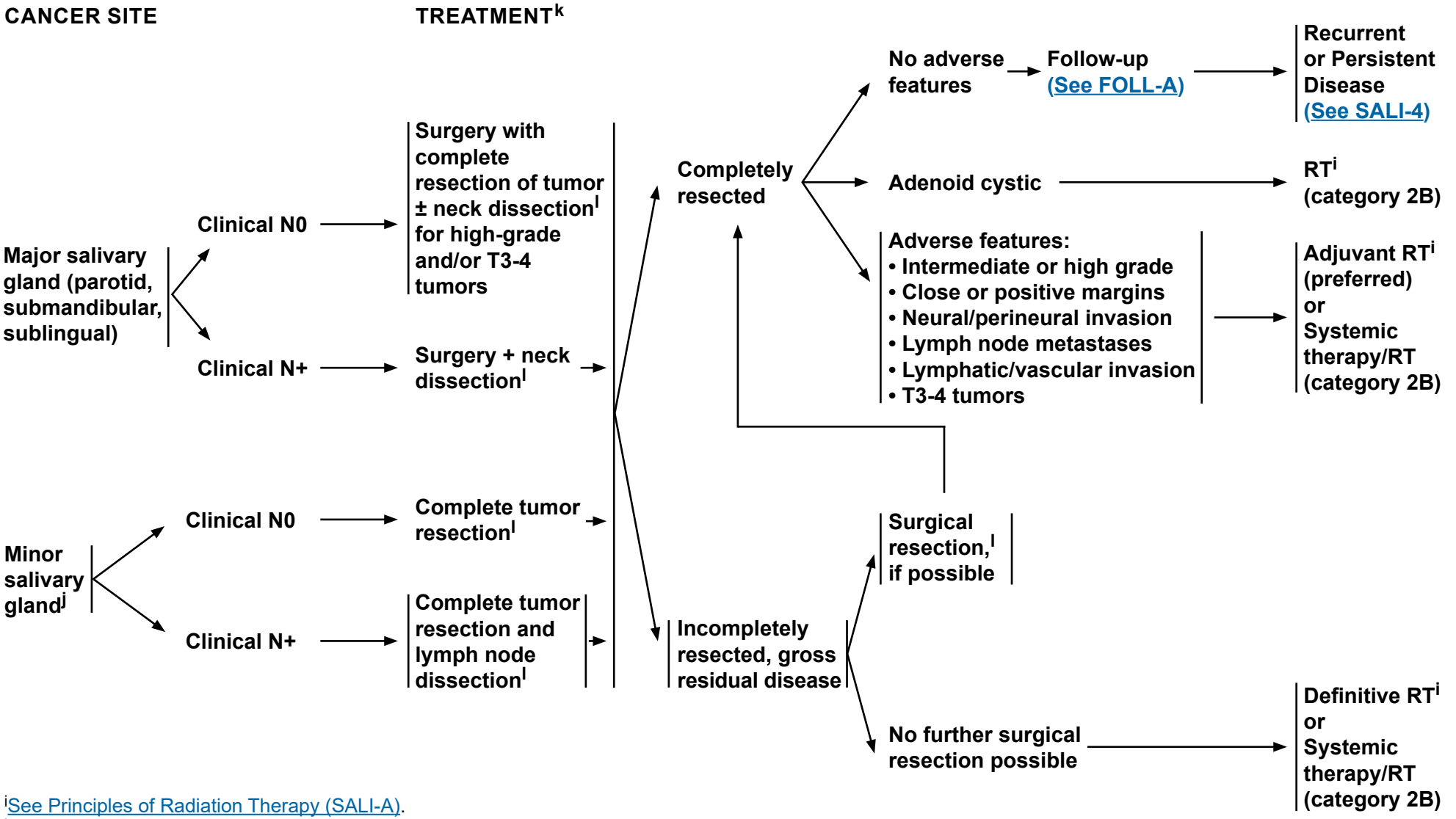

[i] See Principles of Radiation Therapy (SALI-A).
[j] For submandibular and sublingual gland tumors, complete gland and tumor resection is recommended.
[k] The facial nerve should be preserved if possible; strongly consider referral to a specialized center with reconstructive expertise.
[l] See Principles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

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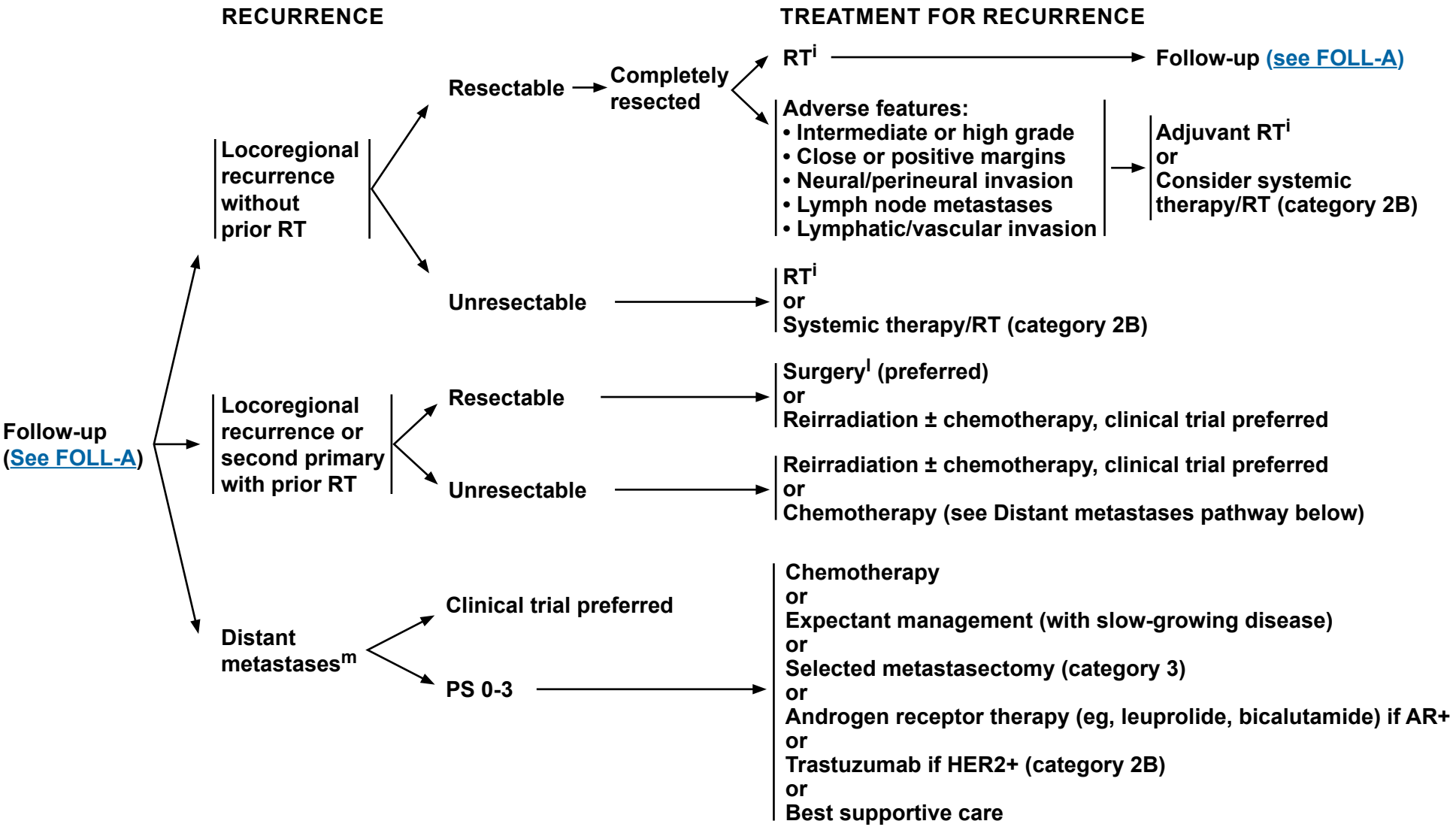

[i] See Principles of Radiation Therapy (SALI-A).
[l] See Principles of Surgery (SURG-A).
[m] Check androgen receptor (AR) status and HER2 status prior to treatment for distant metastases.

PS = Performance Status (ECOG)

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PRINCIPLES OF RADIATION THERAPY[1,2,3]

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[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]**

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)[5]**

Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

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

[2] Neutron therapy was historically considered a promising solution for unresectable salivary gland cancers, but this therapy is currently offered at only one center in the United States. 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] In general, the reirradiated population of head and neck cancer patients described in 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. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)

[4] 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.

[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).

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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 CT (with or without contrast) as clinically indicated**
- **Consider FDG-PET/CT or chest/abdominal/pelvic CT with contrast, and brain MRI (with and without contrast) to rule out metastatic disease**

Multidisciplinary consultation as clinically indicated

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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NCCN Guidelines Version 2.2018
Mucosal Melanoma

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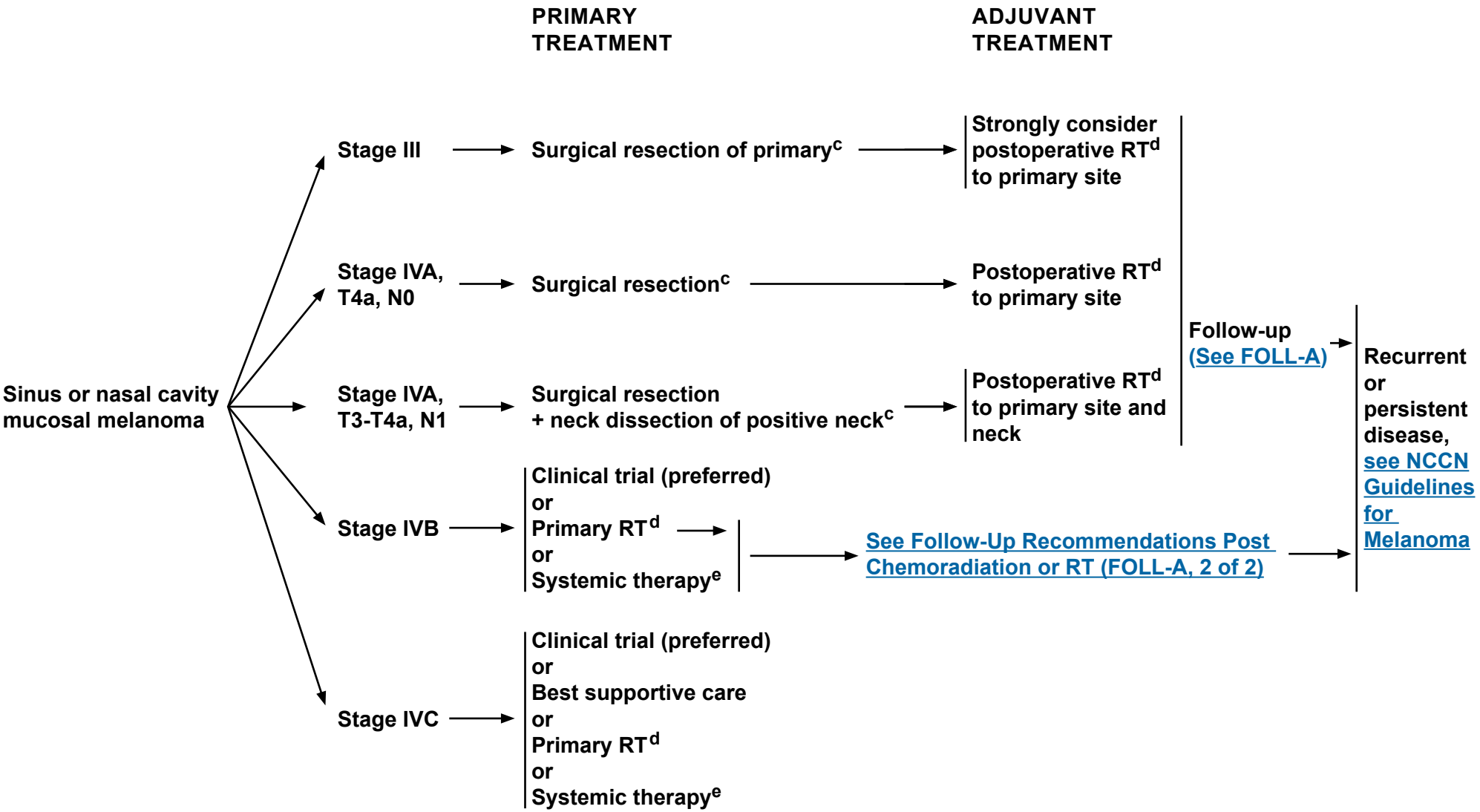

[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MM-A).
[e] See Systemic Therapy for Metastatic or Unresectable Disease (page ME-H) from the NCCN Guidelines for Melanoma.

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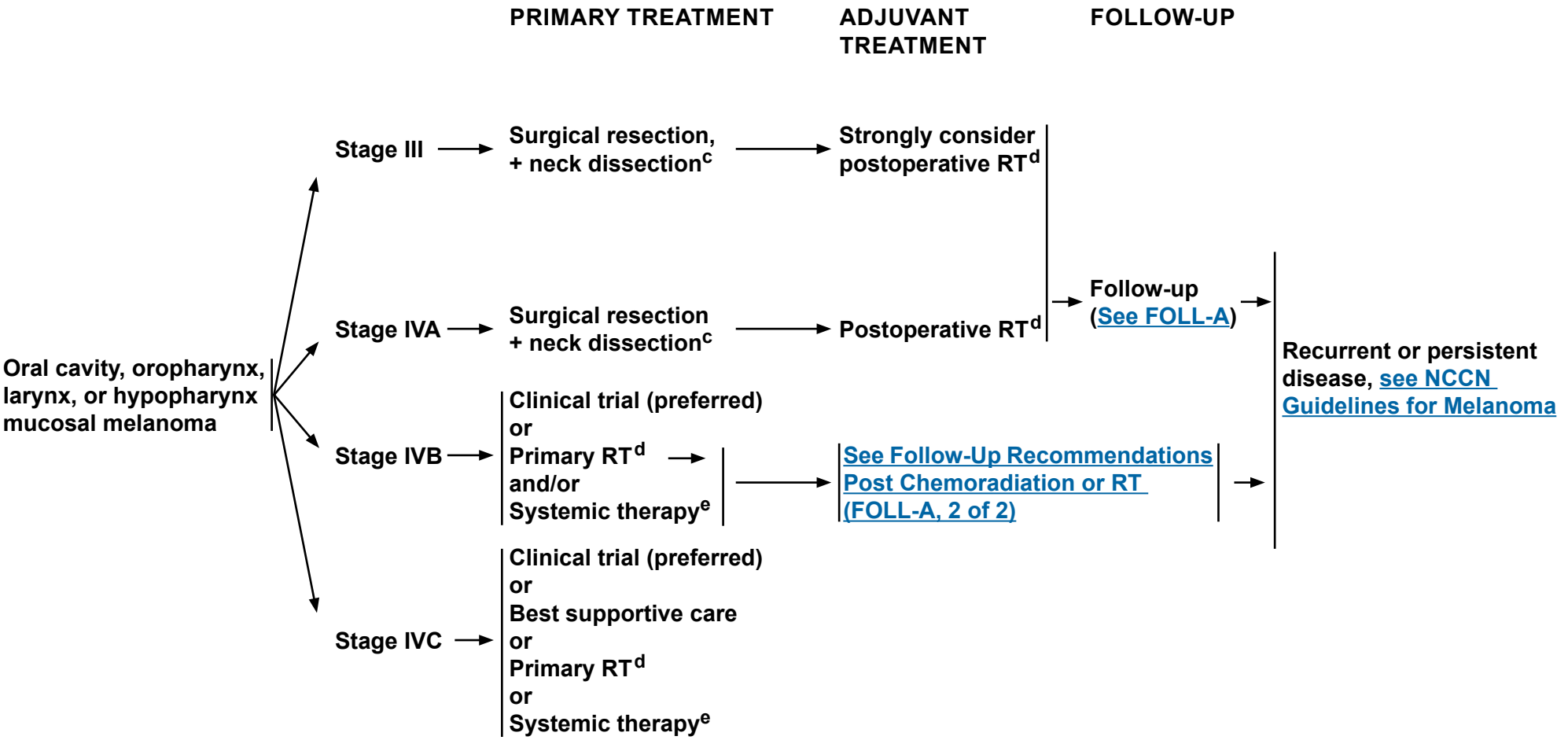

[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MM-A).
[e] See Systemic Therapy for Metastatic or Unresectable Disease (page ME-H) from the NCCN Guidelines for Melanoma.

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

[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MM-A).
[f] High-risk: adverse features: >2 nodes, single node >3 cm, extranodal extension, recurrence in nodal basin after previous surgery.

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PRINCIPLES OF RADIATION THERAPY[1,2]

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 (1.6–1.8 Gy/fraction)**
- **Palliative RT doses and schedules may be considered.**
- **Optional dosing schedules may be considered.[3]**

POSTOPERATIVE:

RT:

- **Preferred interval between resection and postoperative RT is <6 weeks.**
- **PTV**
  - **High risk: adverse features >2 nodes, single node >3 cm, extranodal extension, 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)**
- **Optional dosing schedules may be considered.[3]**

Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

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

[2] Recent studies suggest that increased toxicity may occur when RT is used in combination with BRAF inhibitors. (Anker CJ, Grossmann KF, Atkins MB, et al. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: Consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). Int J Radiat Oncol Biol Phys 2016;95:632-646.)

[3] 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; and mirror and fiberoptic examination):[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**
- **Imaging:**
  - **Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 mo of treatment (category 2B).**
  - **Chest CT with or without contrast as clinically indicated for patients with smoking history (See NCCN Guidelines for Lung Cancer Screening).**
  - **Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination.**
  - **Routine annual imaging (repeat use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.**
- **Thyroid-stimulating hormone (TSH) every 6–12 mo if neck irradiated.**
- **Dental evaluation[3] for oral cavity and sites exposed to significant intraoral radiation treatment.**
- **Consider EBV DNA monitoring for nasopharyngeal cancer (category 2B).**
- **Supportive care and rehabilitation:**
  - **Speech/hearing and swallowing evaluation[4] and rehabilitation as clinically indicated.**
  - **Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is stabilized.[4]**
  - **Ongoing surveillance for depression (See NCCN Guidelines for Distress Management).**
  - **Smoking cessation[5] and alcohol counseling as clinically indicated.**
- **Integration of survivorship care and care plan within 1 year, complementary to ongoing involvement from a head and neck oncologist (See NCCN Guidelines for Survivorship).[6]**

[1]Most recurrences are reported by the patient.
[2]For mucosal melanoma and paranasal sinus cancers, a physical exam should include endoscopic inspection for paranasal sinus disease.
[3]See Principles of Dental Evaluation and Management (DENT-A).
[4]See Principles of Nutrition: Management and Supportive Care (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]Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA Cancer J Clin 2016;66:203-239.

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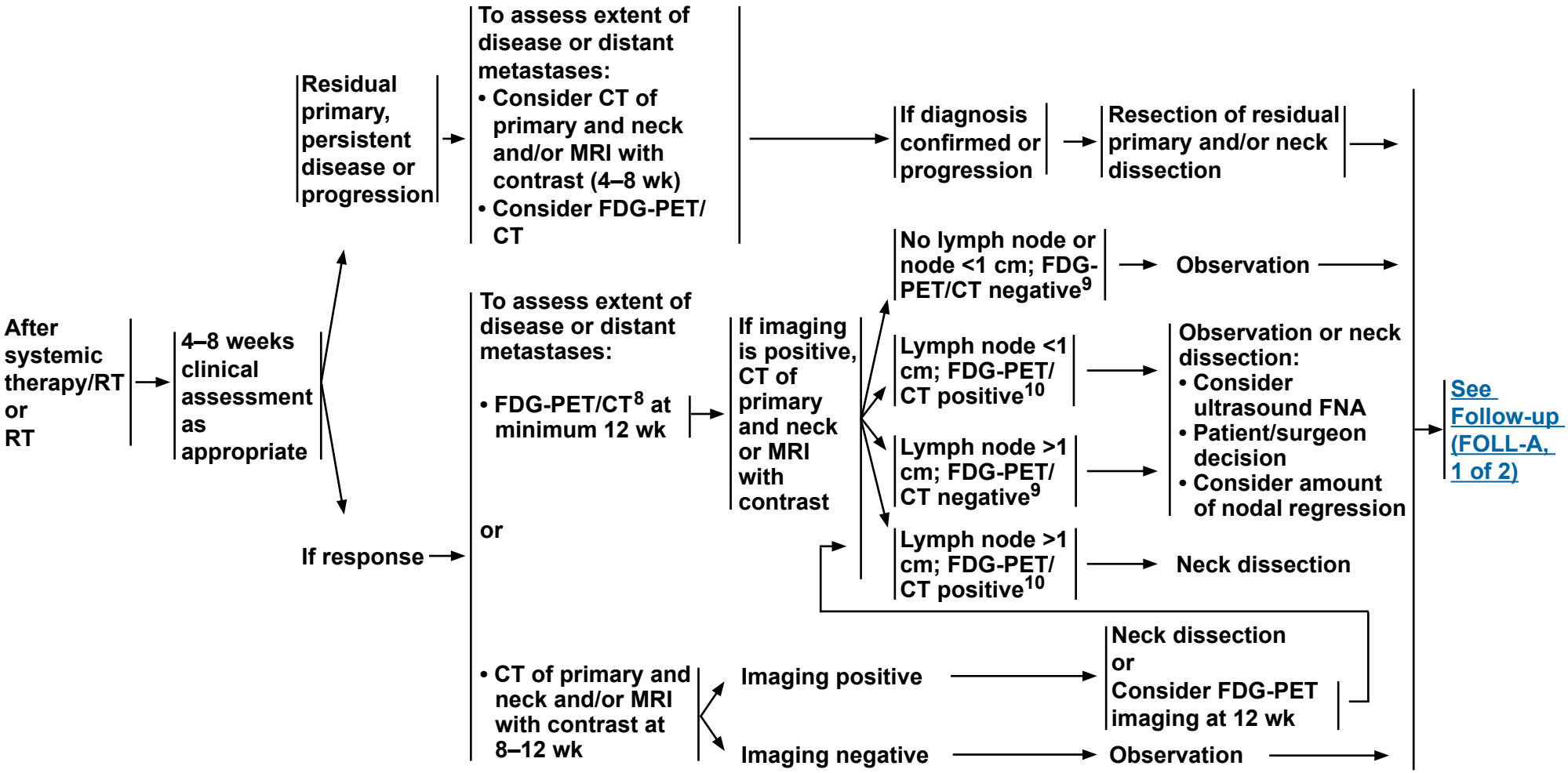
FOLLOW-UP RECOMMENDATIONS POST CHEMORADIATION OR RT NECK EVALUATION[7]



[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.

Continued

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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.**

Continued

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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. If carcinoma in situ is present and if additional margins can be obtained that is the favored approach. Carcinoma in situ should not be considered an indication for concurrent postoperative chemoradiation.**
- **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, hypopharynx, nasopharynx, 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 alveolus that approximate or cross the midline should undergo contralateral selective/modified neck 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, SLN 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**

Continued

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PRINCIPLES OF SURGERY

Neck Management (continued)

- **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. For advanced glottic and hypopharyngeal cancers treated with primary surgery, a level VI dissection (including pretracheal lymph nodes, the delphian lymph node, and unilateral or bilateral paratracheal lymph nodes) and hemithyroidectomy to total thyroidectomy is appropriate. For primary subglottic tumors or glottic cancers with significant subglottic extension, a level VI dissection with unilateral or total thyroidectomy is considered appropriate based on the extent of the primary tumor. For example, a T4a glottic tumor with extension through the cricothyroid membrane and subglottic extension should include a total thyroidectomy and pretracheal and bilateral paratracheal lymph node dissection. Parathyroid glands should be preserved in situ or auto transplanted as indicated.**

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 (3D conformal RT, helical tomotherapy, volumetric modulated arc therapy [VMAT], and proton beam therapy [PBT]) 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.

Advanced radiation therapy technologies such as IMRT, image-guided radiation therapy (IGRT), and PBT may offer clinically relevant advantages in specific instances to spare important organs at risk (OARs), such as the brain, brain stem, cochlea, semicircular canals, optic chiasm and nerves, other cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone (skull base and mandible), pharyngeal constrictors, larynx, and esophagus, and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. The demonstration of significant dose-sparing of these OARs reflects best clinical practice.

Since the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in local tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, and other imaging modalities facilitate target definition. Image guidance is required to provide assurance of accurate daily delivery.

Randomized studies to test these concepts are unlikely to be done since the above specific clinical scenarios are relatively rare. In light of that, the modalities and techniques that are found best to reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.

*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*

Intensity-Modulated Radiation Therapy (IMRT)

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

IMRT, PBT, and Fractionation[10-12]

A number of ways exist to integrate IMRT or PBT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (66–72 Gy to gross disease; 44–63 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/wk) and the "6 fractions/wk accelerated" schedule.[5] The Sequential (SEQ) 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]

Proton Beam Therapy (PBT)

Achieving highly conformal dose distributions is especially important for patients whose primary tumors are periocular in location and/or invade the orbit, skull base, and/or cavernous sinus; extend intracranially or exhibit extensive perineural invasion; and who are being treated with curative intent and/or who have long life expectancies following treatment. Nonrandomized single institution clinical reports and systematic comparisons demonstrate safety and efficacy of PBT in the above-mentioned specific clinical scenarios.[29-49] Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

*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 3D Conformal RT, IMRT, and SBRT

- 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/wk 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 3D Conformal RT, SBRT, PBT, or IMRT[17-28]

- 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.
- Radiation volumes should include known disease only. There is no need to treat prophylactic regions.
- When using SBRT techniques selection of patients who do not have circumferential carotid involvement is advised.
- For 3D conformal RT and IMRT: Standard dosing is 59.4–60 Gy at 1.8–2 Gy/fraction. Hyperfractionated schedule is 60 Gy at 1.2–1.5 Gy/fraction.
- Current SBRT schedules being used or investigated are in the range of 30–44 Gy using 5 fractions.
- 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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RADIATION TECHNIQUES (References)

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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 preferred 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 in randomized studies.**
- **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 for oropharynx, hypopharynx, or larynx; category 2B for lip, oral cavity, ethmoid sinus, maxillary sinus, occult primary)**
  - **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[13-18] (category 1 for high-risk** non-oropharyngeal cancers)**

Nasopharynx:

- **Chemoradiation followed by adjuvant chemotherapy**
  - **Cisplatin + RT followed by cisplatin/5-FU[19-20] or carboplatin/5-FU[21] (category 2B for carboplatin/5-FU)**
- **Cisplatin + RT without adjuvant chemotherapy (category 2B)[22]**

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

- **Induction*/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[23-25] (category 1 if induction is chosen)**
  - **Paclitaxel/cisplatin/infusional 5-FU[26]**
  - **Following induction, agents used with concurrent chemoradiation typically include weekly carboplatin, weekly cisplatin (category 2B), or weekly cetuximab[1,27,28]**

Nasopharynx:

- **Induction/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[29]**
  - **Docetaxel/cisplatin (category 2B)[30]**
  - **Cisplatin/5-FU[24]**
  - **Cisplatin/epirubicin/paclitaxel**
  - **Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[20] or carboplatin[27]**

*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)
**Adverse features: extranodal extension and/or positive margins.

Continued

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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)

- **First-Line Combination Therapy Options:**
  - **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 or carboplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)**
  - **Cisplatin or carboplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)**
  - **Cisplatin/gemcitabine[39,40] (category 1) (nasopharyngeal)**
  - **Carboplatin/cetuximab[41] (nasopharyngeal)**
- **First-Line Single-Agent Options:**
  - **Cisplatin[33,42]**
  - **Carboplatin[43]**
  - **Paclitaxel[44]**
  - **Docetaxel[45,46]**
  - **5-FU[42]**
  - **Methotrexate[47,48]**
  - **Cetuximab[49] (non-nasopharyngeal)**
  - **Gemcitabine[50] (nasopharyngeal)**
  - **Capecitabine[51]**
- **Second-Line Therapy or Subsequent Therapy Options:**
  - **Combination therapy options listed above**
  - **Single-agent options listed above**
  - **Nivolumab[52] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 1)**
  - **Pembrolizumab[53-55]**
    - ◊ **Non-nasopharyngeal: if disease progression on or after platinum-containing chemotherapy**
    - ◊ **Nasopharyngeal: if previously treated, PD-L1-positive recurrent or metastatic disease (category 2B)**
  - **Afatinib[56] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 2B)**

See References

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

Most head and neck cancer patients lose weight and are nutritionally compromised 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). A registered dietitian and a speech language/swallowing therapist should be part of the multidisciplinary team for treating patients with head and neck cancer throughout the continuum of care.

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 for either:**
    1) patients with speech and/or swallowing dysfunction; or
    2) 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 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.**
- **Pain**
  - **Assess pain from oral mucositis and prescribe gabapentin[4] or doxepin[5] as clinically indicated.**

Continued

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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.**

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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 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**

Continued

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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

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

PRINCIPLES OF DENTAL EVALUATION AND MANAGEMENT
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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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 Oral Cavity (including mucosa of lip) (8th ed., 2017)

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) DOI is depth of invasion and not tumor thickness
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm *or* tumor >2 cm but ≤4 cm, and ≤10 mm DOI
T3	Tumor >4 cm *or* any tumor with DOI >10 mm but ≤20 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face)* or extensive tumor with bilateral tongue involvement and/or DOI > 20 mm.
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

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

Regional Lymph Nodes (N)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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Table 1 — Continued

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for the Oral Cavity (including mucosa of lip) (8th ed., 2017)

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included)

Regional Lymph Nodes (N)

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node**,** 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–);*or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension, and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)

Note : A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Prognostic Stage Groups

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

Continued

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Table 2
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasopharynx (8th ed., 2017)
(The following types of cancer are not included: Mucosal melanoma, lymphoma, sarcoma of the soft tissue, bone and cartilage.)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Carcinoma *in situ*
T1	Tumor confined to the nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/ or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)
A grading system is not used for NPCs.

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T0, T1	N1	M0
	T2	N0, N1	M0
Stage III	T0, T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Continued

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Table 3
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Oropharynx (p16-)

TX		Primary tumor cannot be assessed
Tis		Carcinoma *in situ*
T1		Tumor 2 cm or smaller in greatest dimension
T2		Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3		Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4		Moderately advanced or very advanced local disease
	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 the larynx.

Hypopharynx

TX		Primary tumor cannot be assessed
Tis		Carcinoma *in situ*
T1		Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2		Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3		Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4		Moderately advanced or very advanced local disease
	T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle 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.

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Table 3 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N)†	
Clinical N (cN) - Oropharynx (p16-) and Hypopharynx	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	**M**etastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

†A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Continued

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Table 3 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N)†:
Pathological N (pN) - Oropharynx (p16-) 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 smaller in greatest dimension and ENE(−))
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

†Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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

Prognostic Stage 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	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0, N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Continued

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Table 4

American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative [p16-] cancers of the oropharynx)

Primary Tumor (T)

T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*

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

Regional Lymph Nodes (N)
Clinical N (cN)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)

NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0, T1, T2	N0,N1	M0
Stage II	T0, T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage III	T0, T1, T2, T3	N3	M0
	T4	N0, N1, N2, N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0, T1, T2	N0, N1	M0
Stage II	T0, T1, T2	N2	M0
	T3, T4	N0, N1	M0
Stage III	T3, T4	N2	M0
Stage IV	Any T	Any N	M1

Continued

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Table 5

American Joint Committee on Cancer (AJCC) TNM Staging System for the Larynx (8th ed., 2017)

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone and cartilage, and mucosal melanoma of the lip and oral cavity are not included)

Primary Tumor (T)

TX Primary tumor cannot be assessed

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, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage

T4 Moderately advanced or very advanced

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

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

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, cricoid cartilage, 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 and/or inner cortex of the thyroid cartilage

T4 Moderately advanced or very advanced

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

Continued

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Table 5 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Regional Lymph Nodes (N)*		
Clinical N (cN)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2		Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2a	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
	N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3		Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in any lymph node(s) with clinically overt ENE(+)
	N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)

*Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L)
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)

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Table 5 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Pathological N (pN)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); *or* metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−) N2c Metastasis
N2c Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3 Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes and any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)
N3b Metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); or a single contralateral node of any size and ENE(+)

*Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L)
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)

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

Prognostic Stage 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	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Continued

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Table 6
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasal Cavity and Paranasal Sinuses (8th ed., 2017)
(Mucosal melanoma of the nasal cavity and paranasal sinuses are not included)

Primary Tumor (T)

TX Primary tumor cannot be assessed

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

T4 Moderately advanced or very advanced local disease

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 (V2), 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

T4 Moderately advanced or very advanced local disease

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 (V2), nasopharynx, or clivus

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Table 6 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasal Cavity and Paranasal Sinuses (8th ed., 2017)
(Mucosal melanoma of the nasal cavity and paranasal sinuses are not included)

Regional Lymph Nodes (N)		
Clinical N (cN)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2		Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
	N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in any node(s) with clinically overt ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
	N3b	Metastasis in any node(s) with clinically overt ENE (ENE_c)

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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Table 6 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasal Cavity and Paranasal Sinuses (8th ed., 2017)
(Mucosal melanoma of the nasal cavity and paranasal sinuses are not included)

Regional Lymph Nodes (N)

Pathological N (pN)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(–);
	N2a	Metastasis in single ipsilateral node 3 cm or less in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
	N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(–)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); or a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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Table 6 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasal Cavity and Paranasal Sinuses (8th ed., 2017)
(Mucosal melanoma of the nasal cavity and paranasal sinuses are not included)

Prognostic Stage Groups

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

Distant Metastasis (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1 Distant metastasis

Histologic Grade (G)

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

Continued

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Table 7

American Joint Committee on Cancer (AJCC)

TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)

(Squamous cell carcinoma and salivary gland carcinoma of all head and neck sites except HPV-related oropharynx cancer, nasopharynx cancer, melanoma, thyroid carcinoma, and sarcoma. Staging of the patient who presents with an occult primary tumor and EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is also included.)

Regional Lymph Nodes (N)

Clinical N (cN): For patients who are treated with primary nonsurgical treatment without a cervical lymph node dissection.

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2		Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
	N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or metastases in any node(s) with clinically overt ENE(+) (ENE_c)**
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in any node(s) with clinically overt ENE(+) (ENE_c)**

*Midline nodes are considered ipsilateral nodes.

**ENEc is defined as invasion of skin, infiltration of musculature, dense tethering or fixation to adjacent structures, or cranial nerve, brachial plexus, sympathetic trunk, or phrenic nerve invasion with dysfunction Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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Table 7 — Continued

American Joint Committee on Cancer (AJCC)

TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)

(Squamous cell carcinoma and salivary gland carcinoma of all head and neck sites except HPV-related oropharynx cancer, nasopharynx cancer, melanoma, thyroid carcinoma, and sarcoma. Staging of the patient who presents with an occult primary tumor and EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is also included.)

Regional Lymph Nodes (N)

Pathological N (pN): For patients who are treated surgically with a cervical lymph node dissection.

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2a	Metastasis in a single ipsilateral node 3 cm or less in greatest dimension and ENE(+); or a single ipsilateral node larger than 3cm but not larger than 6 cm in greatest dimension and ENE(-)
	N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or metastases in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; or a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; or a single contralateral node of any size and ENE(+)

Anatomic Stage/Prognostic Groups

Stage III	T0	N1	M0
Stage IVA	T0	N2	M0
Stage IVB	T0	N3	M0
Stage IVC	T0	Any N	M1

*Midline nodes are considered ipsilateral nodes

**ENE detected on histopathologic examination is designated as ENEmi (microscopic ENE ≤ 2 mm) or ENEma (major ENE > 2 mm). Both ENEmi and ENEma qualify as ENE(+) for definition of pN.

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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Table 8
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Major Salivary Glands (8th ed., 2017)
(Parotid, Submandibular, and Sublingual)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension without extraparenchymal extension*
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor larger than 4 cm and/or tumor having extraparenchymal extension*
T4	Moderately advanced or very advanced disease
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)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension and ENE(-); or metastases in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) with clinically overt ENE(+)

Note : A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)

Continued

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Table 8 — Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Major Salivary Glands (8th ed., 2017)
(Parotid, Submandibular, and Sublingual)

Regional Lymph Nodes (N)

Pathological N (pN)

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 smaller in greatest dimension and ENE(-)
N2		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2a	Metastasis in a single ipsilateral lymph node 3cm or smaller in greatest dimension and ENE(+) or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
	N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2c	Metastasis in bilateral or contralateral lymph node(s), none more than 6 cm in greatest dimension and ENE(-)
N3		Metastasis in a lymph node, more than 6 cm in greatest dimension and ENE(-) or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+) ; or a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+); or a single contralateral node of any size and ENE(+)

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
	T0, T1, T2, T3	N1	M0
Stage IVA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note : A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)

Continued

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Table 9
American Joint Committee on Cancer (AJCC)
TNM Staging System for Mucosal Melanoma of the Head and Neck (8th ed., 2017)

Primary Tumor (T)

T3 Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx

T4 Moderately advanced or very advanced 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

Histologic Grade (G)

No recommended histologic grading system at this time.

Prognostic Stage Groups

No prognostic stage grouping is proposed at this time.

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Discussion

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 indicated.

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 (see Figure 1); occult primary cancer, salivary gland cancer, and mucosal melanoma (MM) are also addressed.[1,2] Much recent progress has been made during the last 10 years in understanding the epidemiology, pathogenesis, and management of head and neck (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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Head and Neck Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of H&N cancers published between June 26, 2016 and May 30, 2017, using the following search terms: (head and neck cancer) OR (lip cancer) OR (oral cavity cancer) OR (oropharynx cancer) OR (hypopharynx cancer) OR (nasopharynx cancer) OR (larynx cancer) OR (paranasal tumor) OR (ethmoid sinus tumor) OR (maxillary sinus tumor) OR (salivary gland tumor) OR (mucosal melanoma head) OR (mucosal melanoma neck). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[4]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Incidence and Etiology

In 2018, it is estimated that about 64,690 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur, which account for about 3.7% of new cancer cases in the United States.[5] An estimated 13,740 deaths from H&N cancers will occur during the same time period.[5] 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 Infection

Human papillomavirus (HPV) infection is well-accepted as a cause of squamous cancers of the oropharynx (particularly cancers of the tonsils

and tongue base),[6-13] and emerging evidence shows that HPV infection may also be associated with increased risk of squamous cell carcinoma of the larynx.[14] 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.[15] Patients with HPV-associated H&N cancer tend to be younger.[13,16] Oral HPV type 16 infection increases risk of oropharyngeal cancer,[6,12,17,18] and a strong causal relationship has been established.[6,17] HPV types 18, 31, and 33 are responsible for the vast majority of the remaining fraction.[13] Expression of HPV E6 and E7 oncogenes inactivates the tumor-suppressor proteins p53 and pRb, respectively, which leads to development of cancer.[19] Though some non-oropharyngeal cancers are HPV-related,[14,20-22] there is currently insufficient evidence to recommend HPV testing in H&N cancers that are non-oropharyngeal. Analyses from the National Health and Nutrition Examination Survey (2011–2014), including 2,627 adults ages 18 to 33, showed that HPV vaccination was associated with reduced oral HPV prevalence (0.1% in vaccinated individuals vs. 1.6% in unvaccinated individuals; $P = .008$).[23] Further studies are warranted to investigate the efficacy of HPV vaccines in the prevention of oral HPV infections.

Analyses from clinical trials indicate that patients with locally advanced HPV-positive H&N cancers have improved response to treatment and survival (overall survival [OS] and progression-free survival [PFS]) when compared with HPV-negative tumors.[24-29] Treatment response is improved in patients receiving both chemoradiation[24,25] and conventional radiation therapy.[30] A meta-analysis including 18 studies with 4424 patients with squamous cell carcinoma of the H&N showed that patients with tumors that are both HPV-positive and p16-positive had better 5-year OS and 5-year DFS, compared to patients with tumors that are HPV-negative/p16-negative, HPV-positive/p16-negative, and HPV-negative/p16-positive.[31] However, patients with tumors that are HPV-negative/p16-positive had greater 5-year OS, compared to patients with tumors that are p16-negative (regardless of HPV status). Analyses of non-oropharyngeal squamous H&N cancers have shown mixed results regarding whether or not p16-positive disease is associated with better prognosis.[32,33]

The relationship between HPV and other prognostic or predictive factors such as smoking history and stage has been investigated.[34,35] For example, analyses of patients with oropharyngeal cancer who were enrolled in RTOG 9003 or 0129 ($n = 165$) showed that smoking was associated with decreased OS and PFS, regardless of p16 status.[34] A retrospective analysis from a clinical trial showed no difference in the presence of distant metastasis in patients with p16-positive disease, relative to patients with p16-negative disease.[24] Additional analyses have suggested that individuals with matted nodes or N2c disease may have worse prognosis, and therefore should be excluded from deintensification trials.[36-38]

Staging

Stage at diagnosis predicts survival rates and guides management in patients with H&N cancers. The 2017 AJCC staging classification (8th edition) is used as a basis for NCCN's treatment recommendations for H&N cancers.[39] The TNM staging systems developed by the AJCC for the oral cavity and mucosa of the lip, nasopharynx, hypopharynx, p16-negative oropharynx, p16-positive oropharynx, larynx (glottis and supraglottis), paranasal sinuses (ethmoid and maxillary), major salivary glands (parotid, submandibular, and sublingual), and MM are shown in Tables 1 to 8, respectively.[39] In general, stage I or II disease defines a relatively small primary tumor with no nodal involvement. Stage III or IV cancers generally 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.

Management Approaches

Treatment is complex for patients with H&N cancers. The specific site of disease, stage, and pathologic findings guide treatment (eg, the appropriate surgical procedure, radiation targets, dose and fractionation, indications for systemic therapy). 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 two most commonly employed modalities, surgery and RT, result in similar survival in these individuals. The choice of surgery or RT is often based on local institutional expertise and/or perceived relative morbidity of these treatment options. With evolving techniques of systemic therapy/RT and less invasive surgery, morbidity is also a moving target. 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 (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*). 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. Patients treated at high-volume centers tend to have better outcomes relative to patients treated at low-volume centers.[40-42]

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.[43,44] Similarly, managing and preventing sequelae after radical surgery, RT, and systemic therapy (eg, pain, lymphedema of the neck, xerostomia, speech and swallowing problems, depression) requires professionals familiar with the disease.[45-47] Follow-up for these sequelae should include a comprehensive H&N examination and supportive care and rehabilitation.[43] 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 registered dietitian (see *Principles of Nutrition: Management and Supportive Care* in the NCCN Guidelines for Head and Neck Cancers and this Discussion).[48] Dental care for RT effects should be provided (see *Principles of Dental Evaluation and Management* in the NCCN Guidelines for Head and Neck Cancers and this Discussion). 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, available at www.NCCN.org).[49-52] Specific components of patient support and follow-up are listed in the algorithm (see *Team Approach* in the NCCN Guidelines for Head and Neck Cancers). Panel members also recommend referring to the NCCN Guidelines for Palliative Care, Adult Cancer Pain, and Smoking Cessation as needed (available at www.NCCN.org).

Tobacco use is associated with at least 30% of cancer deaths.[53] Therefore, patients' tobacco use history should be assessed. Patients

should 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.[54,55] Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (www.smokefree.gov/). Follow-up care may include chest CT (with or without contrast) for patients with a smoking history (see NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).

Resectable Versus Unresectable Disease

The term *unresectable* has resisted formal definition by H&N cancer specialists. The experience of the surgeon and the support available from reconstructive surgeons, physiatrists, and prosthodontists often strongly influence recommendations, especially in institutions where only a few patients with locally advanced H&N cancers are treated. The NCCN Member Institutions have teams experienced in the treatment of H&N cancers and maintain the multidisciplinary infrastructure needed for reconstruction and rehabilitation. A patient's cancer is deemed unresectable if H&N surgeons at NCCN Member Institutions do not think they can remove all gross tumor on anatomic grounds or if 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 (see *Principles of Surgery* in the NCCN Guidelines for Head and Neck Cancers). 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 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 systemic therapy 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.

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.[56,57] 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,[57-63] and comorbidity also influences costs of care, utilization, and quality of life.[64-66] Traditional indices of comorbidity include the Charlson Comorbidity Index[67] and the Kaplan-Feinstein Index and its modifications.[57,68] The Adult Comorbidity Evaluation-27 (ACE-27) is specifically for H&N cancers and has excellent emerging reliability and validity.[69,70]

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 (ie, 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.[71]

Patient-completed scales should be used to measure quality of life.[72] Three validated and accepted measures for H&N cancer-specific issues are: 1) the University of Washington Quality of Life scale (UW-QOL);[73] 2) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-H&N35);[74] and 3) the Functional Assessment of Cancer Therapy Head and Neck module (FACT-H&N).[75] The Performance Status Scale is a clinician-rated performance scale that is widely used for patients with H&N cancers.[76]

Head and Neck 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. Minimally invasive surgery may be useful for decreasing morbidity.[77,78] 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.[79,80] Evaluation, integration of therapy, assessment of resectability, principles for primary tumor resection, margins, surgical management of the neck and the cranial nerves (VII, X–XII), management of recurrences, and principles for surveillance (including post-treatment neck evaluation) are discussed in the algorithm (see *Principles of Surgery* in the NCCN Guidelines for Head and Neck Cancers).[81,82]

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.*[83] A *comprehensive* neck dissection is one that removes all lymph node groups that would be included in a classic radical neck dissection. Whether the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve is preserved does not affect whether the dissection is classified as comprehensive. Depending on the site, comprehensive neck dissection is often recommended for N3 disease (see the algorithm for specific sites and *Neck Management* in *Principles of Surgery* in the NCCN Guidelines for Head and Neck Cancers).

Selective neck dissections have been developed based on the common pathways for spread of H&N cancers to regional nodes (see Figure 2).[84,85] Depending on the site, selective neck dissection is often recommended for N0 disease (see the algorithm for specific sites and *Neck Management* in *Principles of Surgery* in the NCCN Guidelines for Head and Neck Cancers). 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).[83,86] 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.[83] 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).[87-89]

The chief role of selective neck dissections in these NCCN Guidelines is to determine which patients are candidates for possible adjuvant therapy (ie, systemic therapy/RT or RT), although selective neck dissections may be used as treatment when neck tumor burden is low.[90] 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.[91-93] In the NCCN Guidelines, patients with cervical node metastases who undergo operations with therapeutic intent are generally treated with comprehensive neck dissections, because they often 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.[81] 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 surgery for relapsed/refractory disease (and neck dissection as indicated) is performed. After either RT or chemoradiation, post-treatment evaluation with imaging (ie, CT and/or MRI with contrast, FDG PET/CT) guides the use of neck dissection (see *Follow-Up Recommendations: Post Chemoradiation or RT Neck Evaluation* in the NCCN Guidelines for Head and Neck Cancers).[94-98] 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.[95,99] A meta-analysis including 23 studies of FDG PET/CT showed good diagnostic performance, with sensitivity and specificity values for detection of recurrence of H&N cancer being 0.92 (95% CI, 0.90–0.94) and 0.87 (95% CI, 0.82–0.90), respectively.[100] PET/CT surveillance in patients with advanced nodal disease who received systemic therapy/RT yields a comparable survival rate and quality of life and may be more cost effective, relative to planned neck dissection.[101,102] However, a prospective study including 125 patients with locally advanced H&N cancer who were treated with concurrent systemic therapy/RT showed that the sensitivity of FDG PET/CT for detecting residual disease decreases between 9 (83.3%) and 12 months (59.7%) after primary treatment.[103] A retrospective study showed that PET/CT without contrast was not significantly less accurate than PET/CT with contrast regarding screening for a local or regional recurrence or distant metastasis.[104] Therefore, contrast enhancement may not be necessary as part of post-treatment PET/CT; if PET/CT results are positive, then cross-sectional imaging with contrast enhancement is recommended.

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);[94,105] 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.[94,105,106] In patients who have a clinically negative neck, a negative PET/CT is 90% reliable and further imaging is optional.[107-109] 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.[94] For patients with

more equivocal PET/CT scan results in the neck, a prospective 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.[110]

Postoperative Management of High-Risk Disease

Many factors influence survival and locoregional tumor control in patients with H&N cancers. The role of systemic therapy/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.[111,112] A combined analysis of data from the 2 trials has been done.[113]

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).[112] Note that long-term results from RTOG 9501 have been published.[114] 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 IV and V from an oral cavity or oropharyngeal cancer.[111] The RTOG trial showed statistically significant improvement in locoregional control and disease-free survival (DFS) but not OS, whereas the EORTC trial found significant improvement in survival and the other outcome parameters.

In a randomized phase III trial from a single institution in India, cisplatin 30 mg/m^2 weekly was compared to cisplatin 100 mg/m^2 every 3 weeks, when given concurrently with RT, in 300 patients with locally advanced squamous cell H&N cancer (93% in the adjuvant setting).[115] Two-year locoregional control was superior in patients randomized to receive cisplatin once every 3 weeks (73.1%), compared to patients randomized to receive weekly cisplatin (58.5%) (HR, 1.76; 95% CI, 1.11–2.79; P = .014). However, patients randomized to receive cisplatin once every 3 weeks developed more severe acute toxicities, compared to patients randomized to receive weekly cisplatin (84.6% vs. 71.6%, respectively, P = .006). The acute adverse events that were significantly more likely to have been reported in patients who received cisplatin once every 3 weeks were hyponatremia, leukopenia, neutropenia, and lymphocytopenia (P < .001 for all). A schedule using cisplatin at 50 mg intravenously weekly has also been shown to improve survival in the adjuvant setting in a randomized trial.[116]

To better define risk, a combined analysis of prognostic factors and outcome from the RTOG 9501 and EORTC 22931 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.[113,114] However, it is important to note that the combined analysis was considered exploratory by the authors.[113] These publications form the basis for the NCCN recommendations regarding adjuvant treatment.

In NCCN Member Institutions, most patients with extranodal extension with or without positive surgical margins receive adjuvant chemoradiotherapy after surgery.[116-122] The presence of other adverse risk factors—multiple positive nodes (without extranodal extension), perineural invasion vascular embolism, lymphatic invasion, pT3 or pT4 primary, and oral cavity or oropharyngeal primary cancers with positive level IV or V nodes—are generally 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 concurrently with postoperative RT compared to RT alone, the NCCN Panel added a recommendation to consider chemoradiation for these features.[111]

In the randomized phase II RTOG-0234 trial, two regimens in patients with stage III and IV squamous cell carcinoma of the H&N were compared: 1) adjuvant chemoradiotherapy with cetuximab and docetaxel, and; 2) adjuvant chemoradiotherapy with cetuximab and weekly cisplatin (N = 238).[123] After a median follow-up of 4.4 years, patients randomized to receive docetaxel experienced a 31% reduction in DFS failure rate (HR, 0.69; 95% CI, 0.50–0.96; P = .01), and a 44% reduction in mortality (HR, 0.56; 95% CI, 0.39–0.82; P = .001). Chemoradiotherapy with cetuximab and docetaxel is continuing to be investigated in a randomized controlled trial (RCT) and is currently not recommended by the NCCN Panel as an adjuvant systemic therapy/RT regimen.[124]

Surgery for Relapsed/Refractory Disease

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 (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers). For patients who do not have a complete clinical response to systemic therapy/RT, 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 surgery in patients with relapsed/refractory disease 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 laryngectomy for relapsed/refractory disease, patients may have a higher incidence of pharyngocutaneous fistula, pharyngeal and stomal stenosis, and other wound complications.[125] 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 techniques such as 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. Principles regarding radiation techniques as described in the NCCN Guidelines for Head and Neck Cancers 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). The maximum dose limits are 70 Gy (2 Gy/fraction) for the following sites: lip, oral cavity, oropharynx,

hypopharynx, glottic larynx, supraglottic larynx, occult primary, salivary gland tumors, and MM. For patients with cancer of the pharynx and who have high-risk subclinical disease, a fractionation schedule of 69.96 Gy at 2.12 Gy/fraction daily (Monday–Friday) for 6 to 7 weeks is recommended.[126]

Although several palliative RT regimens are provided, no single regimen is preferred;[127,128] specific regimens vary widely among NCCN Member Institutions. Any palliative RT regimen that might cause severe toxicities should be avoided. More hypofractionated regimens may be useful for patients with end-stage disease. For example, the QUAD SHOT regimen consists of a dose of 44.4 Gy, delivered in 12 fractions over 3 cycles.[129]

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 systemic therapy (see *Radiation Techniques* in the NCCN Guidelines for Head and Neck Cancers and see the individual *Principles of Radiation Therapy* for each primary site). The demonstration of significant dose sparing of organs at risk (eg, brain, cochlea, optic chiasm and nerves, spinal cord) reflects best clinical practice. Target definition and delineation is crucial, and imaging should be used to ensure accurate radiation delivery.

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).[130-133] 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.[130,134] When using hyperfractionation, high-risk sites generally require up to 81.6 Gy (1.2 Gy/fraction).[130,131] 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 3D conformal RT (3D-CRT) or IMRT is used. For 3D-CRT and sequentially planned IMRT, 44 to 50 Gy (2.0 Gy/fraction) is suggested.[135,136] For IMRT, 54 to 63 Gy (1.6–1.8 Gy/fraction) is suggested.[136-138]

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 extranodal extension), or perineural/lymphatic/vascular invasion. Higher doses of postoperative RT alone (60–66 Gy), or with systemic therapy, are recommended for the high-risk features of extranodal extension and/or positive margins.[113,114,133] 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.[139,140] Especially in RT alone settings, schedules delivering at least 1000 cGy per week are recommended,[141-143] 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.[144,145]

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.[146] A long-term follow-up analysis has also shown a small survival advantage for hyperfractionation (*P* = .05).[147] 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.[148]

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.[130,131,149] After 2 years of follow-up, both accelerated fractionation with a concomitant boost (AFX-C) and hyperfractionation were associated with improved locoregional control and DFS 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 OS with hyperfractionation compared to standard fractionation.[131]

The MARCH meta-analysis, including individual patient data from 15 randomized trials, analyzed the effect of hyperfractionated or accelerated RT on survival of patients with H&N cancers.[150] Standard fractionation constituted the control arm in all of the trials in this meta-analysis.[132] 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.[150] Hyperfractionation was associated with a benefit of 8% after 5 years.[151] However, the GORTEC 99-02 trial reported that altered fractionation did not improve outcomes when compared with conventional fractionation.[152,153] An update to the MARCH meta-analysis, including data from 33 trials, continued to show a survival benefit of hyperfractionation, compared to standard fractionation (HR, 0.83; 95% CI, 0.74–0.92; *P* < .001), in patients with locally advanced squamous cell cancers of the H&N.[154]

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.[150,155,156]

Fractionation in Concurrent Chemoradiation

Panel members do not agree about the optimal radiation dose fractionation scheme to use with concurrent systemic therapy. 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).[24] Other fraction sizes (eg, 1.8 Gy, conventional), other dosing schedules of cisplatin, other single agents, multiagent systemic therapy, and altered

fractionation with systemic therapy have been evaluated alone or in combination. Numerous trials have shown that modified fractionation and concurrent chemotherapy are more efficacious than modified fractionation alone.[156-158] 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 OS between the two arms,[24,159,160] indicating that accelerated fractionation is not more efficacious than conventional fractionation when concurrent chemotherapy is added.

Concurrent chemoradiation increases acute toxicity compared to radiation alone, although an increase in late toxicity beyond that caused by RT alone is less clear.[161-163] Altered fractionation and/or multiagent systemic therapy may further increase the toxicity burden.[164] 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

IMRT

The intensity of the radiation beam can be modulated to decrease doses to normal structures without compromising the doses to the cancer targets.[165,166] Over the last 15 years, IMRT has displaced other techniques in the treatment of most H&N malignancies.[167-173] IMRT is an advanced form of CRT permitting more precise cancer targeting while reducing dose to normal tissues.[136,174-177]

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).[178,179] Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can occur.[179,180] Alternatively, separate dose plans for the low versus higher dose targets can be delivered sequentially (reduce target size and boost) or on the same day as separate fractions in twice-a-day schemas (see *Radiation Techniques* in the NCCN Guidelines for Head and Neck Cancers).[132,176,181,182]

IMRT is now widely used in H&N cancers and is the predominant technique used at NCCN Member Institutions.[183,184] 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.[137,172,185-193] OS is similar between patients treated with IMRT and those receiving conventional RT.[167,186,194,195] A prospective Korean study showed that 3D and IMRT techniques were superior to 2D radiation for both PFS and OS in patients with nasopharyngeal carcinoma (NPC), and IMRT was associated with improved survival in multivariate analysis, particularly in T3-T4 tumors.[196] In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT.[197-200] The application of IMRT to other sites (eg, oral cavity, larynx, hypopharynx, salivary glands) is evolving.[201-208]

IMRT may be useful to preserve the optic pathway in patients with sinonasal malignancies.[185] Retrospective analyses including 2,993 patients who received RT for treatment of H&N cancer showed that patients who received IMRT had a shorter duration of feeding tube placement, compared to those who received 3D RT (P = .03).[209] However, IMRT can create new unexpected acute toxicities to organs radiated in the beam path.[210,211] In addition, the long-term effects, even

with using IMRT, can still result in a substantial decrease in quality of life.[212-217]

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).[172,191,218-221] Reports indicate that xerostomia has decreased due to the transition from older 2D and 3D radiotherapy techniques, such as IMRT.[167,169] Numerous phase II studies show a decrease in late toxicity (xerostomia) without compromising tumor control for nasopharyngeal, sinonasal, and other sites.

Three 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 NPC with conventional RT techniques versus with IMRT.[191] The results showed a statistical improvement in salivary flow and in patient-reported quality-of-life parameters.[191] In the study by Kam et al, patients with NPC were randomly assigned to either IMRT or conventional 2D RT.[172] At one year after treatment, patients in the IMRT arm had significantly lower rates of clinician-rated severe xerostomia than patients in the 2D 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. Finally, data from a phase III randomized trial (PARSPORT) indicate that IMRT decreases xerostomia when compared with conventional RT in patients with non-NPC.[167] 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.

Proton Beam Therapy

At present, proton therapy is the predominant particle therapy under active clinical investigation in the United States.[222-225] Proton therapy has been used to treat oropharyngeal cancers, sinonasal malignancies, adenoid cystic carcinomas, and MMs.[226-231] Proton therapy has typically been used to treat patients with the most challenging disease, for which other RT options were not felt to be safe or of any benefit.[227,230,232]

A systematic review and meta-analysis of non-comparative observation studies concluded that patients with malignant diseases of the nasal cavity and paranasal sinuses who received proton therapy appeared to have better outcomes than those receiving photon therapy.[233] A review of proton therapy in patients with H&N cancers included 14 retrospective reviews and 4 prospective nonrandomized studies.[223] The 2- to 5-year local control rates were as low as 17.5% for T4 or recurrent paranasal sinus cancers and as high as 95% for other types of tumors.

In institutional reports, outcomes for proton therapy have been reported.[223,234-236] Recent reports show that proton beam therapy (PBT) for treatment of sinonasal cancer is associated with good locoregional control, freedom from distant metastasis, and acceptable toxicity.[235,236] Another recent institutional report ($N = 41$) showed that PBT may be associated with greater normal tissue sparing without sacrificing target

coverage, which may be associated with reduced toxicity compared to IMRT.[234]

Results from a retrospective study comparing 40 patients with cancer of the nasopharynx, nasal cavity, or paranasal sinuses who received either PBT or IMRT to the H&N (with or without chemotherapy) showed that PBT was associated with lower mean doses to the oral cavity, esophagus, larynx, and parotid glands, regardless of nodal status and compared to IMRT.[237] PBT was also associated with less dependence on opioid pain medication and gastrostomy tube placement, compared to IMRT.

Occasional fatal outcomes have been reported with proton therapy, including 3 deaths secondary to brainstem injury.[238-240] A report from Japan described long-term toxicities after proton therapy in 90 patients with nasal cavity, paranasal sinus, or skull base malignancies.[241] Late toxicities reached grade 3 in 17 patients (19%) and grade 4 in 6 patients (7%) (encephalomyelitis infection in 2 patients, optic nerve disorder in 4 patients). This rate of grade 3 to 4 late toxicity with protons (19%) was similar to the rate reported for conventional RT with photons (16%).[242] Other clinicians have reported low rates of serious toxicities when using strict dose limits for proton therapy.[227,243] In patients with tumors that are periocular in location and/or invade the orbit, skull base, and/or cavernous sinus, and tumors that extend intracranially or exhibit extensive perineural invasion, as well as in patients being treated with curative intent and/or have long life expectancies, achieving highly conformal dose distributions is crucial.

As described above, nonrandomized institutional reports and a small number of systemic reviews have shown that PBT may be safe to use in some settings. Without high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other modern radiation techniques such as IMRT, particularly with regard to tumor control. An accurate comparison of benefits to other RT options should ideally take place in the controlled setting of randomized clinical trials. An alternative approach may be to develop prospectively maintained databases to raise the quality of institutional reports of clinical experiences.[240] In cancers of the paranasal sinus and salivary glands, as well as MM of the H&N, proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

Brachytherapy

Brachytherapy is now being used less often because of improved local control obtained with concurrent chemoradiation. However, brachytherapy still has a role for lip and oral cavity cancers (see *Principles of Radiation Therapy* in the NCCN Guidelines for Cancer of the Lip and Cancer of the Oral Cavity).[244]

Stereotactic Body Radiation Therapy

Stereotactic body RT (SBRT) is an advanced technique of external beam RT (EBRT) that delivers large ablative doses of radiation. Advantages of SBRT include shorter treatment time, promising local control rates, and acceptable toxicity.[245] There is currently insufficient evidence to recommend SBRT for treatment of H&N cancers, but the NCCN Panel acknowledges that it might be beneficial for palliation or for older adults.[246,247]

Follow-up After RT

For patients whose cancer has been treated with RT, the recommended follow-up (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers) 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 have received neck irradiation; patients are at increased risk of hypothyroidism.[248-250]

Principles of Nutrition and Supportive Care

The *Principles of Nutrition* section in the NCCN Guidelines for Head and Neck Cancers 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.[45,251,252] Patients with H&N cancers are also at risk for dehydration. The multidisciplinary expertise of a registered dietitian and a speech-language/swallowing therapist should be utilized throughout the continuum of care.

Patients who have had significant weight loss (5% body weight loss over 1 month, or 10% body weight loss over 6 months) need nutritional evaluation and close monitoring of their weight to prevent further weight loss.[253,254] In addition, all patients should receive nutritional evaluation before and after treatment to assess the need for interventions (eg, enteral support via feeding tubes).[255-257] 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.[258-261] Evaluation by a speech-language/swallowing therapist is needed before and after treatment to help mitigate potential problems.[262-264] Patients are also at risk for dental problems (see *Principles of Dental Evaluation and Management* in this Discussion and the NCCN Guidelines for Head and Neck Cancers).[45]

Oral mucositis, or tissue damage, is common in patients treated with RT for H&N cancers.[265-270] It causes pain in the mouth and when swallowing, which may affect the ability to eat and drink.[265,267,269,270] Oral mucositis is also associated with breaks and/or delays in treatment, as well as hospitalization.[266,268,270] Oral mucositis may be worse in patients receiving concurrent systemic therapy/RT.[270] The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology have published clinical practice guidelines for treatment of oral mucositis, though there are few high-quality studies in this area.[271] An RCT including 155 patients with H&N cancer undergoing treatment for pain related to oral mucositis showed that patients randomized to receive a doxepin oral rinse reported reduced throat and mouth pain, compared to patients randomized to receive a placebo ($P < .001$).[272] Two small retrospective studies including patients with H&N cancer treated with RT or systemic therapy/RT showed that treatment with gabapentin for pain from oral mucositis is associated with a reduced need for narcotic pain medication and high doses of opioids.[269,273] The panel recommends treatment with doxepin or gabapentin for pain related to oral mucositis, as clinically indicated.

NCCN Panel Members agree that reactive feeding tube placement is appropriate in selected patients with H&N cancers.[252,256] 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).[252,254,274] 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) (see *Principles of Nutrition: Management and Supportive Care* in the NCCN Guidelines for Head and Neck Cancers). 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

Patients with H&N cancers 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.[261,265,275-277] 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.[275,276,278-284] Dental/oral evaluation and management can help decrease dental caries and associated problems such as dentoalveolar infection and osteoradionecrosis.[265,278,284-294]

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.[285] Some of the strategies to decrease oral and dental complications include: 1) decrease dry mouth (eg, by using salivary substitutes and stimulation);[295-299] 2) decrease dental caries (eg, by using topical fluoride);[286,300-303] 3) decrease dentoalveolar infection (eg, with frequent evaluations to detect and treat disease promptly); 4) decrease osteoradionecrosis (eg, by extracting teeth before RT);[304] 5) decrease trismus of the masticatory muscles (eg, by using custom mouth-opening devices to maintain range of motion);[305-307] and 6) have patient undergo evaluations during and after treatment to help minimize complications.[295,296,308,309]

During and after treatment, the goals of dental/oral management include: 1) managing xerostomia; 2) preventing trismus; and 3) detecting and treating oral candidiasis.[285] Additional goals after treatment include: 1) preventing and treating dental caries; 2) preventing postradiation osteonecrosis; and 3) preventing oral candidiasis.[285]

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 (see *Workup* in the NCCN Guidelines for *Cancer of the Lip*). Dental evaluation (dental panoramic x-ray), CT, and/or MRI with contrast is done as clinically indicated to better assess soft tissue or nodal spread or if bone invasion is suspected.

For the 8th edition of the AJCC Staging Manual, cancers of the external vermilion lip are now staged as cutaneous carcinomas of the H&N, given the similarity of these cancers to nonmelanoma skin cancer.[39]

Cancers of the lip mucosa continue to be staged as cancers of the oral cavity (see Table 1). The AJCC TNM staging system reflects tumor size, extension, and nodal disease.[39] 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 (see the NCCN Guidelines for *Cancer of the Lip*).[310-312] 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.[313] Occult cervical metastases are not common in patients with early-stage lip cancer, but sentinel lymph node biopsy (SLNB) has been shown to be feasible and effective in patients who may be at high risk of metastases based on tumor size and depth.[314-316]

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 who are unfit for surgery or who have M1 disease at initial presentation should be treated as for very advanced disease (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*).[313]

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 (see the NCCN Guidelines for *Cancer of the Lip*). 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 (see *Principles of Surgery* in the algorithm).

Radiation Therapy

RT, when used as definitive treatment, may consist of EBRT 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 (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Cancer of the Lip*).[317,318] The conventional fractionation dose required also depends on tumor size, but doses of 66 to 70 Gy are adequate to control high-risk disease (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Cancer of the Lip*).

In the adjuvant setting, simple T1-T2 lesions are generally treated the same as a skin lesion (see NCCN Guidelines for Non-Melanoma Skin Cancers; available at www.NCCN.org). Otherwise, 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

perineural/vascular/lymphatic invasion.[319] The fraction size to the intermediate- and low-risk sites ranges from 44 Gy (2.0 Gy/fraction) to 63 Gy (1.6 Gy fraction.) For these sites of suspected subclinical spread, suggested doses are 44–50 Gy if 3D-CRT is used or 54–63 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 (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

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.

Workup and Staging

Imaging studies to evaluate mandibular involvement and a careful dental evaluation (including jaw imaging with Panorex or CT [with or without contrast], as clinically indicated) are particularly important for staging (see Table 1) and planning therapy for oral cavity cancers in addition to a complete H&N examination, biopsy, and other appropriate studies (see *Workup* in the NCCN Guidelines for *Cancer of the Oral Cavity*). For patients who appear to have stage III to IV disease, FDG PET/CT may alter management by upstaging patients.[320] Nutrition, speech, and swallowing evaluations are recommended for selected at-risk patients (see *Principles of Nutrition and Supportive Care* in this Discussion and in the NCCN Guidelines for Head and Neck Cancers).

Treatment

Surgery and RT are the recommended treatment options for early-stage and locally advanced resectable lesions in the oral cavity. The specific treatment is dictated by the TN stage and, if N0 at diagnosis, by the risk of nodal involvement (see the NCCN Guidelines for *Cancer of the Oral Cavity*). 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 systemic therapy 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 patients with early-stage oral cavity cancers, the recommended initial options are resection (preferred) of the primary tumor or definitive RT. In general, many patients undergo either ipsilateral or bilateral neck dissection, which is guided by tumor thickness. It is debatable whether or not patients with early-stage node-negative oral cavity cancers should receive elective neck dissection. A watchful waiting approach reduces the risks associated with surgery.[321] A meta-analysis including four studies with 283 patients with N0 oral cancer showed that elective neck dissection reduces the risk of disease-specific mortality (RR, 0.57; 95% CI, 0.36–0.89; P = .014 for fixed-effects model; RR, 0.59; 95% CI,

0.37–0.96; *P* = .034 for random-effects model), compared to patients undergoing observation only.[322] A prospective RCT (*n* = 496) showed that patients receiving elective neck dissection had greater rates of OS (80% vs. 67.5%, *P* = .01) and DFS (69.5% vs. 45.9%, *P* < 0.001), relative to patients receiving neck dissection after nodal relapse.[323] Patients who received elective neck dissection were less likely to have experienced nodal recurrence (29.6%), relative to patients who did not (45.1%). Subgroup analyses from this study showed that elective neck dissection may be most beneficial in patients with tumor thickness > 3 mm, though this interaction was not statistically significant (*P* = .12).

SLNB may be used to identify occult cervical metastases (see *Sentinel Lymph Node Biopsy* in the *Principles of Surgery* in the NCCN Guidelines for Head and Neck Cancers).[324-330] SLNB is less accurate for floor of the mouth tumors and should be done in centers with expertise in this technique.[324,325] Some diagnostic agents for use in SLNB in patients with squamous cell carcinoma of the oral cavity have been evaluated (eg, technetium Tc99m tilmanocept),[331,332] but the data are currently too limited for the panel to recommend a specific agent.

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 extranodal extension with or without a positive mucosal margin, postoperative systemic therapy/RT (category 1) is the recommended treatment. For patients with positive margins, re-resection is the preferred option. RT is another option, and systemic therapy/RT may be considered. For patients with other risk features, options include RT or to consider systemic therapy/RT.

For patients with advanced-stage, resected oral cavity cancers who have the adverse pathologic features of extranodal extension with or without a positive mucosal margin, the recommended postoperative adjuvant treatment is systemic therapy/RT (category 1).[111-114,116] Adjuvant treatment options for positive margins are the same, but re-resection is an option if technically feasible, with consideration of subsequent RT. 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, RT alone is recommended, or systemic therapy/RT may be considered (see the NCCN Guidelines for *Cancer of the Oral Cavity*).

Radiation Therapy

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 63 Gy (1.6 Gy/fraction) (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Cancer of the Oral Cavity*). For these sites of suspected subclinical spread, suggested doses are 44–50 Gy if 3D-CRT is used or 54–63 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 (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

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. Oropharyngeal cancer that is p16-positive (ie, HPV-mediated) is a different disease than p16-negative cancer. For example, patients with HPV-associated H&N cancer tend to be younger[13,16] and have an improved response to treatment when

compared with patients with HPV-negative tumors.[24-28,333] To take into account these differences, separate staging criteria were published for p16-negative and p16-positive (ie, HPV-mediated) oropharyngeal cancer in the 8th edition of the AJCC Cancer Staging Manual.[39] In 2018, the panel created separate algorithms for p16-positive (HPV-mediated) oropharyngeal cancer. See the section below on *Staging*.

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 and in the NCCN Guidelines for Head and Neck Cancers). Accurate staging (see Table 3 for p16-negative oropharyngeal cancer and Table 4 for p16-positive oropharyngeal cancer) depends on a complete H&N examination and appropriate imaging studies (see *Workup* in NCCN Guidelines for *Cancer of the Oropharynx*).[39,334] Tumor HPV testing through p16 immunohistochemistry (IHC) is required for cancers of the oropharynx, because prior HPV infection is related to the development of a significant proportion of oropharyngeal cancers (see the following section on *HPV Testing*).

HPV Testing

The attributable fraction for HPV in newly diagnosed oropharyngeal cancer is estimated at 60% to 70% in the United States and parts of the European Union.[15,335-338] There are currently no diagnostic tests with regulatory approval. A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by IHC is a widely available surrogate biomarker that has very good agreement with HPV status as determined by HPV E6/E7 mRNA expression.[339-342] Other tests include HPV detection by polymerase chain reaction (PCR) and in situ hybridization (ISH).[339,341] Sensitivity of IHC staining for p16 and PCR-based assay is high, though specificity is highest for ISH.[341] Analyses of HPV testing methods have shown that sensitivity and specificity of p16 IHC ranges from 94% to 97% and 83% to 84%, respectively, with sensitivity and specificity of HPV16 ISH ranging from 85% to 88% and 88% to 95%.[339,342] The reduced specificity for p16 IHC may be due to the presence of p16-positive tumors that do not have evidence of HPV DNA, while the reduced sensitivity for HPV16 ISH may be due to the presence of other high-risk HPV types in the tumor. Due to variations in sensitivity and specificity values of testing options, multiple methods may be used in combination for HPV detection.[13,341-344] Sufficient pathologic material for HPV testing can be obtained by fine-needle aspiration (FNA).[13,345] Guidelines for HPV testing have also been published by the College of American Pathologists.[346] 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.

Staging

The algorithms in the NCCN Guidelines for Oropharyngeal Cancer reflect the new staging criteria published in the 8th edition of the AJCC Cancer Staging Manual for p16-negative oropharyngeal cancer and p16-positive oropharyngeal cancer.[39] In the updated staging criteria for p16-negative oropharyngeal cancer, separate pathologic criteria are now presented for involvement of regional lymph nodes, since extranodal extension is difficult to accurately capture through the imaging workup that is routinely done for clinical staging.[347] The treatment algorithm for p16-negative disease is divided into three 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: T4b, any N; unresectable nodal disease; unfit for surgery; or M1 disease at initial presentation (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*).

A clinical staging system for p16-positive oropharyngeal cancer was developed using data from 1,907 patients with non-metastatic HPV-positive oropharyngeal cancer from seven cancer centers in Europe and the United States.[348] OS did not significantly differ between T4a and T4b disease (*P* = .41). Five-year OS rates did not significantly differ in patients with N1, N2a, or N2b disease, based on the AJCC 7th edition N classification,[349] so the study investigators reasoned that these patients could be grouped into one category (ie, at least one ipsilateral metastatic node ≤6 cm).

An analysis of 704 patients with resected p16-positive oropharyngeal squamous cell carcinoma from five cancer centers showed that the N-classification system for oropharyngeal cancer that was described in the 7th edition of the AJCC Cancer Staging Manual[349] was not significantly associated with OS.[350] However, patients with 4 or fewer pathologically confirmed metastatic nodes had a higher 5-year OS rate, compared to patients with 5 or more pathologically confirmed metastatic nodes (89% vs. 71%, respectively). The results from this analysis were used to construct a pathologic staging system for patients with p16-positive disease: 1) pT1-T2 and fewer than 5 metastatic nodes; 2) pT1-T2 and more than 4 metastatic nodes; or, pT3-T4 and fewer than 5 metastatic nodes; and 3) pT3-T4 and more than 4 metastatic nodes. The 5-year OS rates for these staging groups were 90% (95% CI, 87%–93%), 84% (95% CI, 77%–90%), and 48% (95% CI, 30%–66%), respectively. Five-year DFS rates for the three staging groups were 86% (95% CI, 82%–90%), 72% (95% CI, 64%–79%), and 40% (95% CI, 24%–56%), respectively. The results from this analysis are consistent with an earlier study that showed that the presence of 5 or more metastatic nodes, but not N-classification, was associated with disease recurrence and survival in 220 patients with surgically resected p16-positive oropharyngeal cancer.[351]

The modifications to the NCCN Guidelines for p16 (HPV)-positive oropharyngeal cancer accommodate the new staging system for p16-positive oropharyngeal cancer. However, the changes are relatively modest, since the staging system changes are based on prognostic models and are not based on prospective data from clinical trials that guide clinical decision-making. Based on differences in features associated with prognosis,[348,350] the staging criteria for p16-positive oropharyngeal cancer differs from staging for p16-negative oropharyngeal cancer in the following ways:[39]

- T4b disease has been removed from the staging criteria for defining the primary tumor
- Criteria for defining nodal involvement (both clinical and pathologic) have been simplified for p16-positive disease. Clinical N staging for p16-positive oropharyngeal cancer is based on lymph node size and laterality, while pathologic N staging is based on number of lymph nodes. Further, pN3 disease has been removed for pathologic N.

The treatment algorithms for p16-positive disease have been divided by the panel into three staging categories: 1) cT1-2, cN0-1 (single node ≤3 cm); 2) cT3-4, cN0-1 (single node ≤3 cm); and 3) any T, cN1 (single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm) or cN2-3. The algorithms in the NCCN Guidelines for p16 (HPV)-positive oropharyngeal cancer incorporate the staging criteria presented in the revised AJCC Cancer Staging Manual[39] based on clinical staging criteria. This is to acknowledge that decision-making is currently frequently based on data from trials that included oropharyngeal as well as other anatomic sites that were staged utilizing AJCC 7th edition nodal staging criteria.[349]

Treatment

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.[352-354] Some clinicians have suggested that less-intense treatment may be adequate for HPV-positive oropharyngeal cancers (ie, deintensification)[37]; however, the available data supporting this assertion are limited by retrospective analyses, variability in HPV testing method used, and short follow-up periods.[37,355-357] Deintensification treatment protocols for HPV-associated locally advanced oropharyngeal cancer are being investigated in ongoing clinical trials (eg, NCT01154920, NCT01706939, NCT01302834, NCT01855451). Strategies under active investigation include reducing or using response-stratified RT dose, using RT alone versus chemoradiation, using less invasive surgical procedures such as transoral robotic surgery, using sequential systemic therapy/RT, and using immunotherapy and targeted therapy agents such as cetuximab.[357-359] Recently reported results from two phase II trials showed that RT deintensification may result in equivalent or similar response in patients with stage III-IV HPV16 and/or p16-positive oropharyngeal cancer, compared to full-dose RT.[360,361] Analyses of quality-of-life outcomes from one of these trials showed that RT deintensification was associated with a quicker and more robust return to baseline-level functioning.[362]

With some exceptions, which are noted in this section below, the treatment algorithms for p16-negative and p16-positive oropharyngeal cancer are identical. There is currently no evidence that the new staging criteria published in the 8th edition of the AJCC Cancer Staging Manual[39] should drive clinical decision-making. The difference between p16-positive and p16-negative oropharyngeal cancer is mainly prognostic.

Panel members urge that patients with HPV-related cancers be enrolled in clinical trials evaluating biological and treatment-related questions.[357,359,363]

Early-stage (T1-2, N0-1 for p16-negative disease; T1-2, N0 or single node ≤3 cm for p16-positive disease) 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.[77,80,364,365] Panel members felt that a third option of RT plus systemic therapy was only appropriate for N1 disease, based on results from the phase III randomized GORTEC trial[161] and retrospective analyses from the National Cancer Database.[366] However, systemic therapy/RT for patients with p16-negative N1 disease is a category 2B option, since the number of patients with T1-T2, N1 disease enrolled in the GORTEC trial is small, and more data from prospective trials are needed. For patients with p16-positive disease, systemic therapy/RT is a category 2B option for T2 disease and the involvement of a single node ≤3 cm. In patients with p16-positive disease, the panel currently does not recommend systemic therapy/RT in patients with T1 disease and a single node ≤3 cm, as the data to support this treatment option in these patients are less strong, relative to p16-negative disease, and are based on analyses with fewer patients (see the NCCN Guidelines for *Cancer of the Oropharynx*).

Research on the impact of adverse features such as extranodal extension and number of involved nodes on outcomes in patients with p16-positive disease who have undergone resection is rapidly evolving. Currently, data from only retrospective trials are available,[35,351,352,367-370] and clinical trials are being conducted to validate the revised AJCC staging[39] for clinical decision-making. Analyses from the RTOG 9501[112] and EORTC 22931 trials[111] showed that extranodal extension is associated with poor prognosis in patients with locally advanced H&N

cancer who have undergone surgical resection.[113] However, in a review of published data from these RCTs, it was noted that these studies did not investigate the impact of HPV or p16 status.[371] In response to this review, the investigators from RTOG 9501 and EORTC 22931 pointed out that the prevalence of HPV-positive/p16-positive tumors was likely to be low in these trials.[372] Other limitations noted in this review included unplanned subgroup analyses, the grouping of multiple H&N subsites, inconsistent quantitative reporting and lack of reporting on tumor and lymph node classification, treatment effect sizes, multivariable analyses, and quality-of-life outcomes. Therefore, the investigators who carried out this review argued that these trials lack the generalizability necessary to rationalize the use of adjuvant systemic therapy/RT in patients with p16-positive disease. Based on this controversy and a lack of high-quality, prospective clinical evidence, this recommendation is a category 2A option for both patients with p16-positive disease and p16-negative disease. Adjuvant systemic therapy/RT remains a category 1 recommendation for patients with other types of H&N cancer who have extranodal extension. Since patients with p16-positive oropharyngeal cancer have a generally favorable prognosis and may live longer, toxicity and quality of life are concerns for these patients.[357,359] On the other hand, recent retrospective analyses including 4,443 patients with HPV-positive oropharyngeal cancer from the National Cancer Database showed that deintensification by using a single primary treatment modality such as definitive RT may be associated with worse treatment outcomes in the long-term.[373] Omitting systemic therapy and administering radiotherapy alone is a category 2B option for patients with p16-positive disease who have extranodal extension following surgery.

For patients with positive margins, re-resection (if feasible), RT (category 2B for patients with p16-positive disease), and systemic therapy/RT are treatment options.[133] For patients with other risk features, options include RT or systemic therapy/RT. For patients with p16-positive disease and other risk features such as perineural invasion, vascular embolism, or lymphatic invasion, systemic therapy/RT is a category 2B option.

For locally advanced resectable disease (T3-4a, N0-1 for p16-negative disease; T3-4, single node ≤3 cm for p16-positive disease; any T, N2-3 for p16-negative disease; or any T with either N2-3, single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm for p16-positive disease), 3 treatment options are recommended (see the NCCN Guidelines for *Cancer of the Oropharynx*), in addition to enrollment in clinical trials. The 3 options are: 1) concurrent systemic therapy/RT;[133,161] 2) transoral or open resection of the primary and neck (with appropriate adjuvant therapy [systemic therapy/RT or RT]); or 3) induction chemotherapy (category 3) (followed by RT or systemic therapy/RT).[77,80,374] Panel recommendations regarding adjuvant therapy for locally advanced disease do not differ between p16-positive and p16-negative oropharyngeal cancer.

Concurrent systemic therapy/RT—with high-dose cisplatin as the preferred systemic agent—is recommended for treatment of locoregionally advanced p16-positive and p16-negative cancer of the oropharynx (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers). 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 and the NCCN Guidelines for *Cancer of the Oropharynx*).[161,375-383]

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 p16-positive and p16-negative oropharyngeal cancer (see the NCCN Guidelines for *Cancer of the Oropharynx*) 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 p16-negative and p16-positive oropharyngeal cancer (ie, T3-4a, N0-1 for p16-negative disease; T3-4, single node ≤3 cm for p16-positive disease; any T, N2-3 for p16-negative disease; or any T with either N2-3, single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm). However in other sites, category 2A and 2B recommendations for induction chemotherapy are common based on the update from RTOG 91-11 (see *Cancer of the Glottic Larynx*, *Cancer of the Supraglottic Larynx*, and *Cancer of the Hypopharynx* in the NCCN Guidelines for Head and Neck Cancers).[215] 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.[375] Residual toxicity from induction chemotherapy may also complicate the subsequent delivery of definitive RT or systemic therapy/RT. For laryngeal cancer, RT alone (category 1) is recommended after a complete or partial response with induction chemotherapy; systemic therapy/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 OS with the incorporation of chemotherapy.[380] However, a change in the pattern of failure with less distant metastases was noted in some studies.[384] Also, a correlation was noted between response to induction chemotherapy and subsequent durable response to radiation.[384,385] 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 OS was not improved. Because total laryngectomy is among the procedures most feared by patients,[386] 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).[384,385] Yet even in this setting, the role of induction chemotherapy decreased with time. Randomized trials and related meta-analyses indicated that concurrent systemic therapy/RT (with cisplatin being the best-studied agent) offered superior locoregional tumor control and survival compared to radiation alone,[387-395] and shorter duration of therapy compared to induction therapy followed by radiation. Meta-analyses reported that

concurrent systemic therapy/RT was more efficacious than an induction chemotherapy strategy.[380,383] 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 relapsed/refractory disease. The concurrent cisplatin/radiation arm had the highest larynx preservation rate (see *Cancer of the Larynx* in this Discussion).[396] A long-term follow-up of 91-11 confirmed that concomitant systemic therapy/RT improved the larynx preservation rate and that induction chemotherapy was not superior to RT alone.[215] However, OS did not differ among the treatment arms.

Nonetheless, interest in the role of induction chemotherapy endures for a few reasons. Advances in surgery, RT, and concurrent systemic therapy/RT have yielded improvements in locoregional 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.[397,398] 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.[399] 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, DFS, or OS, depending on the trial) for patients in the 3-drug induction group compared to those receiving 2 drugs (cisplatin plus 5-FU).[378,379,381,382] A randomized phase III 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.[400,401] A meta-analysis including five RCTs (N = 1,772) showed that the TPF induction chemotherapy regimen was associated with reduced risk of death (HR, 0.72; 95% CI, 0.63–0.83; P < .001) and greater reductions in progression (HR, 0.78; 95% CI, 0.69–0.87; P < .001), locoregional failure (HR, 0.79; 95% CI, 0.66–0.94; P = .007), and distant failure (HR, 0.63; 95% CI, 0.45–0.89; P = .009) compared with cisplatin plus 5-FU.[402]

Whether adding induction chemotherapy to concurrent chemoradiation results in a clear advantage in OS continues to be unclear.[377,403,404] Both the DeCIDE and the PARADIGM trials did not convincingly show a survival advantage with the incorporation of induction chemotherapy.[403,404] In patients with stage III or IV squamous cell H&N cancers, a randomized phase II study compared induction TPF followed by concurrent cisplatin/5-FU with RT versus concurrent cisplatin/5-FU with RT alone. A higher radiologic complete response rate was reported with the incorporation of induction chemotherapy.[405] Results from a larger follow-up study suggest a survival advantage and are currently reported in an abstract.[406] The phase II ECOG-ACRIN trial (E2303) showed promising results in terms of primary site response and survival for cetuximab, paclitaxel, and carboplatin as induction chemotherapy, followed by systemic therapy/RT with the same drug regimen in patients with stage III or IV squamous cell H&N cancers (N = 74),[407] but the incremental benefit of induction chemotherapy requires further validation using randomized design.

After a complete or partial response with induction chemotherapy for patients with laryngeal cancer, RT alone is recommended (category 1);[215] systemic therapy/RT is a category 2B recommendation after a partial response[400,401,408] (see NCCN Guidelines for *Cancer of the Glottic Larynx, Cancer of the Supraglottic Larynx*). After induction

chemotherapy, panel members agree that weekly cetuximab or carboplatin are reasonable agents to use with concurrent radiation.[403,409-411] Of note, investigators in the DeCIDE trial used the combination of docetaxel/hydroxyurea/5-FU with RT after induction chemotherapy in this setting.[404] Weekly cisplatin with RT following induction chemotherapy is a category 2B option, based on extrapolation.[403,410,411] However, because of toxicity concerns, high-dose cisplatin (100 mg/m^2 every 21 days × 3) is not recommended after induction cisplatin-based chemotherapy.[377,410] 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 therapy/RT—high-dose cisplatin preferred—is considered the gold standard by many NCCN Panel Members in several settings (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers).[111-114,387,412] 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.[402] Therefore, when used as induction chemotherapy for oropharyngeal cancer, this regimen is a category 1 recommendation. Paclitaxel, cisplatin, and 5-FU is also an option for induction chemotherapy.[378]

Radiation Therapy Fractionation

The recommended schedules are shown in the algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Cancer of the Oropharynx*). IMRT is preferred, as it may be useful for decreasing toxicity.[413,414] A fractionation schedule of 69.96 Gy at 2.12 Gy/fraction daily (Monday–Friday) for 6 to 7 weeks is recommended for patients with high-risk subclinical disease, consistent with the fractionation schedule used for these patients in RTOG 0615.[126] Moderate acceleration of treatment is acceptable in patients with early-stage oropharyngeal cancer.[133,415]

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

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 3) depends on a complete H&N examination coupled with appropriate studies (see *Workup* in the NCCN Guidelines for *Cancer of the Hypopharynx*).[39] 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 who are amenable to larynx-preserving (conservation) surgery (most T1, N0; selected T2, N0); and 2) those with advanced resectable cancer who

require pharyngectomy with total or partial laryngectomy (T1-4a, any N). The surgery and RT options for the former group (see the NCCN Guidelines for *Cancer of the Hypopharynx*) represent a consensus among the panel members.

Patients with more advanced disease (defined as T1-3, any N)—for whom the indicated surgical option is partial or total laryngopharyngectomy—may be managed with 3 approaches (see the NCCN Guidelines for *Cancer of the Hypopharynx*) in addition to enrollment in clinical trials: 1) induction chemotherapy followed by definitive RT (category 1 for RT) if a complete response was achieved at the primary site[384] or followed by other options depending on the response; 2) surgery with neck dissection, lymph node dissection, and postoperative radiation or chemoradiation as dictated by pathologic risk features; or 3) concurrent systemic therapy/RT (see the NCCN Guidelines for *Cancer of the Hypopharynx*). When using concurrent systemic therapy/RT, the preferred systemic agent is high-dose cisplatin (category 1) (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers). Given the functional loss resulting from this surgery and the poor prognosis, participation in clinical trials is emphasized.

The recommendation of the induction chemotherapy/definitive RT option is based on an EORTC randomized trial.[384] 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 systemic therapy 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.[384] 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 OS rates equivalent to those obtained with induction platinum/5-FU followed by RT.[416,417] However, a long-term update from this trial showed that larynx preservation rate was higher in patients who were randomized to receive the alternating regimen (32%), compared to patients who received the sequential regimen (25%).[417] 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.[400,401]

As noted in the algorithm, surgery is recommended if a partial response or less occurs after induction chemotherapy (see the NCCN Guidelines for *Cancer of the Hypopharynx*). 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 systemic therapy/RT is recommended (category 1) for the adverse pathologic features of extranodal extension and/or positive mucosal margin. For other risk features, clinical judgment should be used when deciding to use RT alone or when considering adding systemic therapy to RT (see the NCCN Guidelines for *Cancer of the Hypopharynx*). Severe late toxicity appears to be associated with the amount of RT.[399]

Options for patients with T4a, any N disease include: 1) total laryngopharyngectomy plus neck dissection plus lymph node dissection followed by adjuvant systemic therapy/RT or RT; 2) enrollment in clinical trials; 3) induction chemotherapy (category 3); or 4) systemic therapy/RT (category 3) (see the NCCN Guidelines for *Cancer of the Hypopharynx*).

Radiation Therapy Fractionation

Fractionation for RT is discussed in the algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Cancer of the Hypopharynx*). A fractionation schedule of 69.96 Gy at 2.12 Gy/fraction daily (Monday–Friday) for 6 to 7 weeks may be used for patients with high-risk subclinical disease, consistent with the fractionation schedule used for these patients in RTOG 0615.[126]

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

Cancer of the Nasopharynx

NPC is a rare cancer, accounting for 0.6% of all cancers diagnosed worldwide in 2012.[418] However, there are areas of the world with endemic disease; global incidence rates are highest in Southeast Asia (especially southern China), Micronesia/Polynesia, Eastern Asia, and North Africa.[418,419] Rates are 2 to 3 times higher in men than in women.[418,419] Among H&N cancers, NPC has one of the highest propensities to metastasize to distant sites. Regional recurrences are uncommon, occurring in only 10% to 19% of patients.[420,421] The NCCN Guidelines for the evaluation and management of NPC provide recommendations aimed at addressing the risks for local, regional, and distant disease.

Workup and Staging

The workup of nasopharyngeal cancer includes a complete H&N examination and other studies (see the NCCN Guidelines for *Cancer of the Nasopharynx*). 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 2017 AJCC staging classification (8th edition) is used as the basis for treatment recommendations (see Table 2).[39]

Epstein-Barr virus (EBV) DNA testing may also be considered (see *Epstein-Barr Virus*, below). HPV infection has been associated with World Health Organization type I NPC in case reports and very small case series, but the limited data regarding the impact on chemoradiation outcomes are conflicting.[422-424] Therefore, routine testing for HPV in NPC is not recommended by the NCCN Panel.

Epstein-Barr Virus

Infection with EBV is an etiologic factor in the development of NPC.[425,426] Workup for NPC may include EBV testing of both the tumor itself and the blood, particularly in the presence of nonkeratinizing and undifferentiated histology.[427-429] Testing methods for detection of EBV in tumor include ISH for EBV-encoded RNA (EBER)[430] and IHC staining

for LMP1.[431] ISH for EBER tends to be a more sensitive testing method for carcinomas, relative to LMP1 IHC staining.[432] PCR may be used to evaluate EBV DNA load in plasma. Sensitivity and specificity values range from 53% to 96%, and 88% to 100%, respectively.[433] Testing for plasma EBV DNA has been used in select centers as a means of residual disease monitoring. For patients with locoregional disease, studies have shown that high initial levels of plasma EBV DNA, or persistently elevated levels near or at the end of radiation therapy, are associated with a significantly poorer outcome following RT or chemoradiation.[434-439] A meta-analysis including 13 studies showed that plasma EBV DNA levels assessed pre-treatment were associated with mortality (HR, 2.81; 95% CI, 2.44–3.24; $P < .001$) and distant metastasis (HR, 3.89; 95% CI, 3.39–4.47; $P < .001$), though these studies were significantly heterogeneous ($P = .03$).[440] Plasma EBV DNA has also been studied as an indicator of disease response to chemotherapy as induction therapy prior to chemoradiation[441] and in the setting of distant metastases.[442]

Treatment

Patients with T1, N0, M0 nasopharyngeal tumors should be treated with definitive RT alone, including elective RT to the neck.

Locoregionally Advanced Disease

The Intergroup trial 0099, which randomly assigned patients EBRT plus chemotherapy versus EBRT alone, closed early when an interim analysis disclosed a significant survival advantage favoring the combined chemotherapy and radiation group.[412] The addition of chemotherapy also decreased local, regional, and distant recurrence rates. Subsequent phase III randomized trials in Asia confirmed that concurrent chemoradiation increased survival when compared with RT alone.[443-445] In one of these trials, 5-year OS was 70% for the chemoradiation group versus 59% for the RT group.[443] The randomized study conducted in Singapore, which was modeled after the Intergroup 0099 treatment regimen, continued to show the benefit of adding chemotherapy to RT. After combined cisplatin and RT, adjuvant cisplatin/5-FU was also given in this trial.[445] This regimen appeared to reduce toxicity while still providing a beneficial antitumor effect. However, a phase III randomized trial from China comparing concurrent cisplatin/RT with (or without) adjuvant cisplatin/5-FU showed that adjuvant chemotherapy did not significantly improve survival following chemoradiation (HR, 0.74; 95% CI, 0.49–1.10; $P = .13$).[446]

An individual patient data meta-analysis by Blanchard et al,[447] which included 19 trials and 4,806 patients with non-metastatic NPC, showed that both adjuvant chemotherapy following chemoradiation and chemoradiation without adjuvant chemotherapy were associated with better OS (HR, 0.65; 95% CI, 0.56–0.76 and HR, 0.80; 95% CI, 0.70–0.93, respectively) and PFS (HR, 0.62; 95% CI, 0.53–0.72 and HR, 0.81; 95% CI, 0.71–0.92, respectively). However, differences between the included studies assessing chemoradiation with and without adjuvant chemotherapy (eg, different length of follow-up, fewer patients with stage II disease in trials assessing adjuvant chemotherapy) limited the ability to make a firm conclusion regarding the efficacy of one treatment modality over the other. A network meta-analysis based on this individual patient data meta-analysis[447] (including 20 trials and 5,144 patients) showed that the addition of adjuvant chemotherapy to chemoradiation was associated with better PFS (HR, 0.81; 95% CI, 0.66–0.98), compared to chemoradiation only.[448] The authors argued that more chemotherapy, in addition to concurrent chemoradiation, could reduce recurrence rates. The NRG-HN001 trial (NCT02135042) is currently in progress to further investigate the role of adjuvant chemotherapy following chemoradiation in patients with locoregionally

advanced NPC; in part, delivery of adjuvant chemotherapy is individualized based on EBV DNA plasma levels.

Induction chemotherapy (prior to concurrent chemoradiation) is also a treatment option for patients with locoregionally advanced NPC. In a recent phase III, randomized, multi-institutional trial from China including 480 patients with stage III-IVb N+ disease, those randomized to receive TPF with concurrent chemoradiation had a better 3-year failure-free survival rate (80%; 95% CI, 75–85) compared to patients who received solely chemoradiation (72%; 95% CI, 66–78) (HR, 0.68; 95% CI, 0.48–0.97; *P* = .034).[449] Grade 4 adverse events occurred in 18% of patients who received induction TPF with concurrent radiotherapy, compared to 1% of patients who received chemoradiotherapy only (*P* < .001), with neutropenia (15%) and leucopenia (5%) being the most common grade 4 adverse events in the induction chemotherapy group. In another randomized trial from China, presently only available in abstract form, patients with stage III-IVb NPC randomized to receive induction cisplatin/5-FU followed by chemoradiation (*n* = 238) had a better 3-year DFS rate (82%; 95% CI, 0.77–0.87) compared to patients (*n* = 238) who received chemoradiotherapy only (74%; 95% CI, 0.68–0.80; *P* = .028).[450] Multivariate analyses showed a significant difference between treatment arms for DFS (HR, 0.67; 95% CI, 0.47–0.95; *P* = .023) and distant metastasis-free survival (HR, 0.63; 95% CI, 0.41–0.98; *P* = .038). However, OS was not significantly better in patients receiving the induction chemotherapy regimen. Finally, in a complex randomized trial (including one substudy comparing induction chemotherapy to adjuvant chemotherapy administration, given either before or after definitive chemoradiation), unadjusted comparisons of induction versus adjuvant chemotherapy did not reach statistical significance, but select adjusted comparisons indicated some improvements in disease progression or death associated with assignment to induction.[451]

Taken together, results thus far suggest that induction chemotherapy prior to chemoradiation in patients with locally advanced NPC may potentially impact tumor control, compared to chemoradiation without additional chemotherapy.[448,452] Expert groups (eg, ESMO, NCI) differ in their clinical practice guidelines regarding use of induction chemotherapy for these patients,[453] and the NCCN expert panel could not reach uniform consensus in this regard. Clinical trials are currently ongoing to address the role of induction chemotherapy prior to chemoradiation for patients with locoregionally advanced NPC (eg, NCT01872962, NCT02512315). Currently available evidence shows trends favoring the addition of chemotherapy to concurrent chemoradiation in patients with locoregionally advanced NPC;[448] however, it is unclear whether to administer chemotherapy to these patients before or after chemoradiation.

For patients with locoregionally advanced NPC (T1, N1-3; T2-T4, any N), enrollment in a clinical trial is preferred. The panel recommends concurrent chemoradiotherapy (cisplatin) with adjuvant chemotherapy (cisplatin/5-FU) for locoregionally advanced NPC. Concurrent chemoradiotherapy (cisplatin) without adjuvant systemic therapy is a category 2B recommendation based on a single randomized trial from China, which did not demonstrate a clear superiority over delivery of adjuvant chemotherapy.[446] Cisplatin for chemoradiation is recommended for patients who do not have a contraindication to the drug, because the vast majority of randomized trials support the use of cisplatin in this setting.[412,443] If using adjuvant chemotherapy, adjuvant carboplatin/5-FU is a widely accepted option; however, this recommendation is a category 2B option due to the uncertainty about the benefits of adjuvant chemotherapy for all NPC patients.[454]

Induction chemotherapy (followed by chemoradiation) is also recommended for patients with NPC with either T1, N1-3 or T2-T4, any N lesions. Based on the results from randomized trials[449-451] and a meta-analysis,[448] the panel voted to change the category recommendation for induction chemotherapy followed by chemoradiotherapy from category 3 to category 2A for the 2018 update. Besides TPF, several other induction/sequential chemotherapy regimens are recommended in the algorithm for NPC.[379,411,443,455]

Radiation Therapy Fractionation

For early-stage high-risk NPC, radiation doses of 66 to 70.2 Gy given with standard fractions are necessary for control of the primary tumor and involved lymph nodes (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Cancer of the Nasopharynx*). Radiation dose-fractionation schedules may vary slightly depending on institutional preference. Usually, these deliver between 2.0 to 2.12 Gy/fraction daily (Monday–Friday) for 33 to 35 fractions to all areas of gross disease to a total dose of approximately 70 Gy.[126] Low-risk subclinical disease in the low neck is often treated with 44 to 54.1 Gy at 1.64 to 2.0 Gy/fraction, and for intermediate-risk disease 59.4 to 63 Gy in 1.8 to 2.0 Gy/fraction is often given with dose-painting to different regions of the skull base and neck.

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers). Since the deep areas of the skull base may be inaccessible to clinical examination, periodic cross-sectional imaging may be necessary. The clinical benefit of blood EBV DNA monitoring is currently uncertain (see *Epstein-Barr Virus*, above), but it may be considered (category 2B).

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. 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. In contrast, 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.

Workup and Staging

The evaluation of the patient to determine tumor stage is similar for glottic and supraglottic primaries (see *Cancer of the Glottic Larynx* and *Cancer of the Supraglottic Larynx* in the NCCN Guidelines for Head and Neck Cancers). Multidisciplinary consultation may be indicated for both sites because of the potential for loss of speech and, in some instances, for swallowing dysfunction (see *Principles of Nutrition: Management and Supportive Care* in the NCCN Guidelines for Head and Neck Cancers). The 2017 AJCC staging classification (8th edition) for laryngeal primary tumors is determined by the number of subsites involved, vocal cord mobility, extranodal extension, and the presence of metastases (see Table 5).[39]

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 patients with carcinoma in situ of the larynx, recommended treatment options include: 1) endoscopic removal (ie, stripping, laser), which is preferred; or 2) RT.[456,457] For early-stage glottic or supraglottic cancer, a systematic review published in 2009 showed that surgery or RT have similar effectiveness[458] (see *Cancer of the Glottic Larynx* and *Cancer of the Supraglottic Larynx* in the NCCN Guidelines for Head and Neck Cancers), though the quality of studies comparing the effectiveness of RT and surgery in early laryngeal cancer is low.[459] A more recent meta-analysis including 11 studies showed that OS (P = .04) and laryngeal preservation (P < .001) were both better in patients who were treated with transoral laser microsurgery, compared to patients treated with RT.[460] The choice of treatment modality depends on anticipated functional outcome, the patient's wishes, reliability of follow-up, and general medical condition.[461] 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 should be evaluated before surgery. Adjuvant treatment depends on the presence or absence of adverse features. Adjuvant treatment for highly selected patients with T1-2, N0 supraglottic cancer may include re-resection if there are positive margins.

Resectable, advanced-stage glottic and supraglottic primaries are usually managed with a combined modality approach (see *Cancer of the Glottic Larynx* and *Cancer of the Supraglottic Larynx* in the NCCN Guidelines for Head and Neck Cancers). If total laryngectomy is indicated but laryngeal preservation is desired, concurrent systemic therapy/RT is recommended, based on results from Intergroup trial RTOG 91-11.[215,396] When using systemic therapy/RT, high-dose cisplatin (category 1) is preferred (at 100 mg/m^2 on days 1, 22, and 43).[215]

Induction chemotherapy with management based on response is an option 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).[215] 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 and the NCCN Guidelines for *Cancer of the Glottic Larynx* and *Cancer of the Supraglottic Larynx*).[215] Definitive RT (without systemic therapy) is an option for patients with T3, N0-1 disease who are medically unfit or refuse systemic therapy (see *Cancer of the Glottic Larynx* and *Cancer of the Supraglottic Larynx* in the NCCN Guidelines for Head and Neck Cancers). Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after systemic therapy/RT or RT, or for those patients who develop a subsequent locoregional recurrence (see *Post-Chemoradiation or RT Neck Evaluation* in *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

Concurrent RT and systemic therapy (eg, cisplatin 100 mg/m^2 preferred [category 1]) is the recommended option for achieving laryngeal preservation.[215,396]

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) for relapsed/refractory disease 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 recommended treatment 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.[396] 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.[215] OS 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 recommended treatment approach is total laryngectomy with thyroidectomy and neck dissection as indicated (depending on node involvement) followed by adjuvant treatment (RT, or systemic therapy/RT may be considered)[462] (see *Cancer of the Glottic Larynx, Cancer of the Supraglottic Larynx,* and *Principles of Surgery* in the NCCN Guidelines for Head and Neck Cancers). For patients with glottic T4a larynx cancer, lymph node dissection may also be done, if indicated, and 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.[215,396]

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers). 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.[349] Note that the workup for patients with suspected paranasal sinus tumors includes a complete H&N CT with contrast or MRI with contrast; dental/prosthetic and multidisciplinary consultations are recommended if clinically indicated. FDG PET/CT may be considered in the workup of patients with clinically apparent stage III or IV disease.

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, or sinonasal neuroendocrine carcinoma [SNEC]).[463-466] The defining features of esthesioneuroblastoma, SNUC, and SNEC continue to be debated,[467] and patients diagnosed with these diseases should be referred to a center of expertise and encouraged to enroll in clinical trials. Locoregional control and incidence of distant metastasis are dependent on T stage, N stage, and tumor histology.[468] However, T stage remains the most reliable predictor of survival and locoregional control (see Table 6).[39] MM also occurs in the paranasal sinus region, nasal cavity, and oral cavity (see *Mucosal Melanoma of the Head and Neck* in this Discussion and the NCCN Guidelines for *Mucosal Melanoma*). Biopsy results may also indicate that patients have sarcoma or lymphoma (see the NCCN Guidelines for Soft Tissue Sarcoma and Non-Hodgkin's Lymphomas, available at www.NCCN.org).[469,470]

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. Nodal involvement is rare in ethmoid sinus tumors, and lymph node metastasis is associated with poor prognosis.[471] Patients with ethmoid sinus cancer who have N+ neck disease should undergo neck dissection with appropriate risk-based adjuvant therapy. Patients with high-grade tumors have worse survival outcomes following surgery, compared to patients with low-grade tumors.[472]

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 (see the NCCN Guidelines for *Ethmoid Sinus Tumors*). If no adverse pathologic factors are found, this treatment may obviate the need for postoperative RT in T1 patients only (category 2B). Postoperative systemic therapy/RT may also be considered in patients with high-risk pathologic features, such as positive margins, high-grade lesions, and intracranial extension (category 2B). 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. For patients with high-risk subclinical disease, doses greater than 70 Gy may be used, with a modified fractionation (eg, <2.0 Gy/fraction) for at least part of treatment to minimize toxicity. Radiation therapy fractionation for patients with ethmoid sinus tumors is described in the *Principles of Radiation Therapy* in the NCCN Guidelines for *Ethmoid Sinus Tumors* (see also *Head and Neck Radiation Therapy* in this Discussion).

Systemic therapy/RT may be used to preserve the orbital organs and avoid surgery in patients with T4 disease.[473,474] Systemic therapy should be part of the overall treatment for patients with SNUC, small cell, or SNEC histologies.[475-484] Surgery and RT have been used to treat patients with esthesioneuroblastomas; systemic therapy has also been incorporated into the locoregional treatment.[483-489] Long-term follow-up is necessary for esthesioneuroblastomas, because recurrence can even occur after 15 years.[483,490,491]

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 (see the NCCN Guidelines for *Maxillary Sinus Tumors*).[242,492-494] However, definitive RT or systemic therapy/RT is recommended for T4b, any N, although this is a category 2B recommendation for patients with T3-4a, N0 disease.[495] Studies using IMRT have shown that it reduces the incidence of complications, such as radiation-induced ophthalmologic toxicity; however, the 5-year OS rate has not improved.[192,242,496-499] Radiation therapy fractionation for patients with maxillary sinus tumors is described in the *Principles of Radiation Therapy* in the NCCN Guidelines for *Maxillary Sinus Tumors* (see also *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 (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

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 at initial presentation (M1); 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. Combination regimens recommended by the panel for recurrent, unresectable, or metastatic disease are as follows: 1) cisplatin/docetaxel/cetuximab (for non-nasopharyngeal cancer);[500] 2) cisplatin/paclitaxel/cetuximab (for non-nasopharyngeal cancer);[501,502] and 3) cisplatin/gemcitabine (for nasopharyngeal cancer).[503] For the cisplatin/docetaxel/cetuximab regimen, the median PFS was 7.1 months and OS was 15.3 months; 1-year OS was 58.6%. This newer taxane-based regimen has impressive OS and is an option for patients with good PS. Carboplatin combined with a taxane and cetuximab was also added as a treatment option for recurrent, unresectable, or metastatic disease in 2017. However, the preferred treatment option 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).[504] Results from a trial that compared 5 different cisplatin-based regimens for nasopharyngeal cancer showed that a cisplatin/gemcitabine regimen was effective although not better than either cisplatin/5-FU or cisplatin/paclitaxel.[503]

The treatment of patients with unresectable, persistent, recurrent, or metastatic H&N cancers should be dictated, in large part, by the patient's performance status (PS) (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*). Patients should be fully informed about the goals of treatment, cost of combination systemic therapy, and potential for added toxicity.

Newly Diagnosed Advanced Disease

Many randomized trials[116,387-391,505-508] and meta-analyses of clinical trials[380,392-395] show significantly improved OS, DFS, and local control when a concomitant or alternating systemic therapy 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 (see *Principles of Radiation Therapy* in the NCCN Guidelines for *Very Advanced Head and Neck Cancers*).[133,387]

Bonner et al randomly assigned 424 patients with locally advanced and measurable stage III to IV squamous cell carcinomas of the hypopharynx, oropharynx, and larynx to receive definitive RT with or without cetuximab.[509] Locoregional control and median OS (49 months vs. 29.3 months, *P* = .03) were significantly improved in patients treated with RT and cetuximab compared to RT alone. Five-year OS in these patients was 45.6% in patients treated with RT and cetuximab and 36.4% in patients who received RT alone (HR, 0.73; 95% CI, 0.56–0.95; *P* = .018).[510] However, in a report of secondary analyses from this trial including only patients with cancer or the larynx or hypopharynx (*n* = 168), investigators failed to find a statistically significant difference between the two groups for laryngeal preservation, laryngectomy-free survival, and median OS.[511] Nevertheless, trial results show that 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 (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers).[152,512,513] A phase II randomized trial (*N* = 70) in which cisplatin and cetuximab, combined with RT, were compared showed that toxicity was significantly increased in patients randomized to receive cetuximab and RT, compared to patients randomized to receive cisplatin and RT.[514] Limited data are available comparing combination chemoradiation versus using a single agent concurrently with RT. Results of the randomized phase III RTOG 0522 trial showed that the addition of cetuximab to cisplatin and RT did not significantly improve outcomes in patients with stage III or IV H&N cancer (*N* = 891).[515]

For patients with a PS of 0 or 1, the recommended treatment of newly diagnosed, very advanced disease is concurrent systemic therapy/RT (with high-dose cisplatin as the preferred [category 1] systemic agent).[387] Carboplatin/5-FU is another category 1 option.[152] Cetuximab with concurrent RT is a category 1 option for oropharynx, hypopharynx, and larynx; this regimen is a category 2B option for other squamous cell cancer sites of the H&N, based on results from Bonner et al.[510] Other systemic therapy/RT options are listed in the guidelines (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers). 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 also *The Induction Chemotherapy Controversy* in this Discussion).[379,382] Other options for patients with a PS of 2–3 are described in the algorithm (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*). Radiation therapy fractionation for patients with newly diagnosed, very advanced disease is described in the *Principles of Radiation Therapy* in the NCCN

Guidelines for *Very Advanced Head and Neck Cancers*; see also *Head and Neck Radiation Therapy* in this Discussion).

Metastatic Disease

For patients with metastatic (M1) disease at initial presentation, palliative adjunctive measures include RT to areas of symptomatic disease, analgesics, and other measures to control other manifestations of disease spread (eg, hypercalcemia). Locoregional treatment prior to beginning systemic therapy may be considered. Single agents and combination systemic therapy regimens are both used (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers).[516] Unless otherwise specified, regimens or single agents can be used for either nasopharyngeal or non-nasopharyngeal cancer (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers). Response rates to single agents range from 15% to 35%.[501,517,518] Active and more commonly used single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, capecitabine, cetuximab (for non-nasopharyngeal cancer), and gemcitabine (for nasopharyngeal cancer).[501,516,519-531] For the 2017 update, vinorelbine was removed as a single agent option.

Active combination regimens include: 1) cisplatin or carboplatin, plus 5-FU with cetuximab (for non-nasopharyngeal cancer only) (category 1);[504] 2) cisplatin or carboplatin, plus a taxane;[532,533] 3) cisplatin with cetuximab (for non-nasopharyngeal cancer only);[520] or 4) cisplatin with 5-FU.[525,533] These combination regimens, on average, result in a doubling of response rates compared to single agents. 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 OS, for the combination regimen.[519,525,533-535] Historically, the median survival with systemic therapy 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.[525] 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.[533] 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[520] compared cisplatin plus cetuximab versus cisplatin plus placebo as first-line treatment for 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 systemic therapy doublet (10.1 vs. 7.4 months, $P = .04$).[504] 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.[524] Available data for novel agents have not established them as treatment options for recurrent or metastatic H&N cancers outside of a clinical trial.[536,537]

Metastatic Nasopharyngeal Cancer

For patients with nasopharyngeal cancer who present with metastatic disease, enrollment in a clinical trial is preferred. Other recommended initial therapy options include either a platinum-based combination systemic therapy regimen or concurrent systemic therapy/RT; treatment depends on whether disease is localized or widespread and if it is symptomatic or posing a clinical risk to the patient.[412,443,454] Patients who receive chemotherapy alone may receive subsequent RT to the primary and neck or concurrent chemoradiation as clinically indicated. Population-based data appear to support the role of earlier RT in the management of metastatic disease.[538]

Active combination regimens for these patients include gemcitabine/cisplatin (category 1);[539,540] cisplatin or carboplatin, plus a taxane;[532,533] cisplatin/5-FU;[525,533] or carboplatin/cetuximab.[541] Results from a trial that compared five different cisplatin-based regimens for NPC showed that a gemcitabine/cisplatin regimen was effective although not better than either cisplatin/5-FU or cisplatin/paclitaxel.[503] However, results from a recent randomized phase III trial showed that patients with recurrent or metastatic NPC (N = 362) who received gemcitabine/cisplatin had a greater median PFS, compared to patients who received cisplatin/5-FU (7.0 months vs. 5.6 months, respectively; HR, 0.55; 95% CI, 0.44–0.68; P < .001).[540] Gemcitabine/vinorelbine was removed from the list of recommendations for the 2018 update, because there are more data to support use of other regimens. Active and more commonly used single agents are listed in the algorithm (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers).[501,516,519-525,527,528,530,531]

Recurrent or Persistent Disease

Surgery is recommended for resectable recurrent or persistent locoregional disease; adjuvant therapy depends on the risk factors (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*). Consistent with the treatment recommendations for patients with newly diagnosed locally advanced T4b (M0) or unresectable nodal disease and PS 0 or 1, patients with a resectable recurrence or persistent locoregional disease who have not previously been treated with RT may also be treated with concurrent systemic therapy/RT [high-dose cisplatin is the preferred (category 1) systemic agent)[387]]. Induction chemotherapy followed by RT or systemic therapy/RT is a category 3 recommendation for these patients (see *The Induction Chemotherapy Controversy* in this Discussion). If the recurrence is unresectable and the patient did not have prior RT, then RT with concurrent systemic therapy is recommended, depending on the PS (see the NCCN Guidelines for *Very Advanced Head and Neck Cancers*). 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. Locoregional treatment may be considered in the presence of distant metastasis with locoregional failure. Radiation therapy fractionation for patients with recurrent or persistent disease is described in the *Principles of Radiation Therapy* in the NCCN Guidelines for *Very Advanced Head and Neck Cancers*; see also *Head and Neck Radiation Therapy* in this Discussion).

The management of patients with recurrent or persistent nasopharyngeal cancer is described in the algorithm (see NCCN Guidelines for *Very Advanced Head and Neck Cancers*). Unless otherwise specified, combination regimens or single agents can be used for either nasopharyngeal or non-nasopharyngeal cancer (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers). Combination therapy options include: 1) cisplatin or carboplatin with docetaxel or paclitaxel; 2) cisplatin/5-FU; 3)

cetuximab/carboplatin; and 4) gemcitabine/cisplatin (category 1).[503,539,541] Results from a randomized phase III trial showed that patients with recurrent or metastatic NPC (*N* = 362) who received gemcitabine/cisplatin had a greater median PFS, compared to patients who received cisplatin/5-FU (7.0 months vs. 5.6 months, respectively; HR, 0.55; 95% CI, 0.44–0.68; *P* < .001).[540] For those who have failed platinum-based therapy, options are listed in the algorithm (see *Principles of Systemic Therapy* in the NCCN Guidelines for Head and Neck Cancers).[528]

Reirradiation

Reirradiation may be done in patients with recurrent H&N cancer, using 3D-CRT, IMRT, PBT, or SBRT. A randomized phase III multicenter trial in France (*N* = 130) showed that reirradiation combined with systemic therapy in patients with a resectable recurrence improves DFS, compared to patients receiving only surgery (HR, 1.68; 95% CI, 1.13–2.50; *P* = .01).[542] However, toxicity of this regimen was considerable, with grade 3 of 4 acute toxicity (mucositis/pharyngitis) in 28% of patients.

Advanced RT techniques may be used for reirradiation. A retrospective review of 227 patients who were treated at an NCCN Member Institution showed that IMRT-based reirradiation of the H&N may be associated with local control and improved survival rates, but toxicity rates were considerable, with adverse events grade 3 or higher occurring in 32% of patients at 2 years and 48% at 5 years.[543] Use of concurrent systemic therapy was associated with greater risk of toxicity. Use of particle therapy (eg, use of photon or proton therapy) may be associated with reduced mean dose to organs at risk.[544] Retrospective studies show that PBT used for reirradiation may be associated with good outcomes (eg, 65%–84% OS, improved locoregional control and freedom from distant metastasis) and acceptable toxicity.[545,546] However, in one retrospective study, 3 patients died (out of 60), possibly due to reirradiation-related effects.[546] SBRT with or without cetuximab following surgery for relapsed or refractory disease has been investigated in an institutional report (*N* = 28).[547] Rates for 1-year local control, distant control, DFS, and OS were 51%, 90%, 49%, and 64%, respectively, and adverse events grade 3 or higher were rare. SBRT for reirradiation should not be used in patients with circumferential carotid involvement, and dosing schedules may include 30 to 44 Gy in 5 fractions.

The decision to treat with reirradiation should take into account comorbidity, the toxicity of previous treatment methods, and the amount of time that has passed since previous treatment.[548-550] Treatment planning should take spinal cord limits into account so that the safest maximum dose is delivered.[548,551,552] PBT may be used for reirradiation when normal tissue constraints cannot be met by photon-based therapy.[543,545,546]

Dosing schedules that may be used for reirradiation are described in *Radiation Techniques* in the NCCN Guidelines for Head and Neck Cancers. Radiation volumes should include known disease only; prophylactic treatment is not needed. There are currently knowledge gaps regarding appropriate use of irradiation, and patients should be encouraged to enroll in clinical trials.[543,548]

Disease That Has Progressed on or After Platinum-containing Chemotherapy

Afatinib, a TKI, is a second-line systemic therapy option for non-nasopharyngeal persistent H&N cancer or cancer that has progressed on or after platinum-containing chemotherapy (category 2B). This addition was based on results of the phase III LUX-Head & Neck 1 RCT in which afatinib was compared to methotrexate in patients with

recurrent or metastatic H&N cancer who had progressed on or after platinum-based therapy (*N* = 483).[553] Patients randomized to receive afatinib had greater PFS, relative to patients randomized to receive methotrexate (2.6 months vs. 1.7 months; *P* = .03). Grade 3 or 4 adverse events reported in patients receiving afatinib were rash or acne (10%), diarrhea (9%), stomatitis (6%), and fatigue (6%). Neutropenia was reported in one patient.[553] Subgroup analyses from this trial showed that outcomes did not differ between older and younger patients, indicating that afatinib may be safely used in older adults, though the PFS benefit seemed to be most clear in the HPV-negative group.[554] A randomized phase II trial comparing afatinib to cetuximab in patients with recurrent or metastatic H&N cancer who had progressed on or after platinum-based therapy (*N* = 121) showed comparable response rates between the two drugs, though more patients randomized to receive afatinib discontinued treatment due to drug-related adverse events, relative to patients randomized to receive cetuximab (23% vs. 5%, respectively).[555]

Nivolumab, an anti-PD-1 antibody, was assessed in a phase III RCT including 361 patients with recurrent H&N squamous cell cancer whose disease had progressed within 6 months following platinum-based chemotherapy.[556] With a median follow-up of 5.1 (range 0–16.8) months, the OS was significantly greater in patients randomized to receive nivolumab, compared to patients randomized to receive standard second-line single-agent systemic therapy with either methotrexate, docetaxel, or cetuximab (HR, 0.70; 97.73% CI, 0.51–0.96; *P* = .01). One-year survival was also greater for patients who received nivolumab, relative to patients who received standard therapy (36.0% vs. 16.6%, respectively), and response rate was higher (13.3% vs. 5.8%, respectively), but median PFS was not significantly different between the two groups (2.0 months vs. 2.3 months, respectively; *P* = 0.32). In prespecified exploratory analyses, the OS benefit in the nivolumab-treated patients appeared to be confined to those patients with a tumor PD-L1 expression level of 1% or more (*n* = 149) (8.7 vs. 4.6 months, HR, 0.55; 95% CI, 0.36–0.83). In patients with tumor PD-L1 expression level less than 1% (*n* = 111), no OS advantage was demonstrated for the nivolumab-treated patients (5.7 vs. 5.8 months; HR, 0.89; 95% CI, 0.54–1.45). Grade 3 or 4 treatment-related adverse events occurred in 13.1% of patients who received nivolumab, compared to 35.1% of patients who received standard therapy. Additional prespecified exploratory analyses showed that patient-reported quality-of-life outcomes favored nivolumab over methotrexate, docetaxel, or cetuximab.[557] Taken together, these results indicate that nivolumab prolongs survival in patients with recurrent or metastatic squamous cell H&N cancer that has progressed after platinum-based chemotherapy, relative to patients who receive standard single-agent systemic therapy.

Pembrolizumab, another anti-PD-1 antibody, was initially studied at a dose of 10 mg/kg given every two weeks in the squamous cell H&N cancer cohort of the KEYNOTE-012 trial.[558] Clinical activity was identified, and the possibility that responses could be durable was suggested. A lower, fixed-dose schedule using pembrolizumab 200 mg every 3 weeks was subsequently assessed in a phase 1b expansion cohort of 132 patients with recurrent or metastatic squamous cell H&N cancer.[559] Eighty-two percent of these patients had previously received systemic therapy for their recurrent or metastatic disease. At 6 months, the OS rate was 59%, and the PFS was 23%, with an overall response rate of 18%. Observed responses appeared durable although the follow-up was limited (median 9 months). By scoring both tumor and immune cells, the response rate in patients who were PD-L1–positive (≥1% expression) was

significantly greater than in patients who were PD-L1–negative (22% vs. 4%, respectively, *P* = .021), and responses were seen in both HPV-associated and non-HPV-associated disease. Pembrolizumab was generally well-tolerated, with grade 3-4 toxicities reported in only 9% of patients, and no treatment-related deaths.[558]

Pembrolizumab in patients with PD-L1–positive recurrent or metastatic NPC was assessed in the nonrandomized multi-institutional phase IB KEYNOTE-028 trial (*N* = 27).[560] All of the patients but two had previously received systemic therapy for their recurrent or metastatic disease. The objective response rate (partial response only, since no patients had a complete response) was 26%, with a median duration of response of 17.1 months. The OS rate at 6 and 12 months was 85% and 63% respectively, with PFS rates of 39% and 34%, respectively. About 30% of patients experienced a grade 3-5 drug-related adverse event. The panel voted to include pembrolizumab for patients with previously treated, PD-L1–positive recurrent or metastatic NPC for the 2018 update, but this is a category 2B option based on panel consensus.

The nonrandomized phase II KEYNOTE-055 trial studied pembrolizumab in 171 patients with squamous cell H&N cancer that progressed following treatment with both a platinum and cetuximab.[561] The overall response rate was 16% (95% CI, 11%–23%), and the mean duration of response was 8 months. Grade 3-4 toxicities were reported in 15% of patients, with one treatment-related death.[561]

The panel recommends nivolumab for patients with recurrent or metastatic squamous cell H&N cancer who have progressed on or following platinum-based chemotherapy as a category 1 recommendation based on high-quality evidence,[556] while pembrolizumab is recommended as a category 2a recommendation, based on results from nonrandomized trials.[558,559] Despite the ambiguities of PD-L1 testing and definitions, PD-L1 expression may be associated with better outcomes from treatment with immunotherapy for recurrent or metastatic squamous cell H&N cancer (ie, greater likelihood of response to pembrolizumab and greater survival benefit in response to nivolumab).

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 having 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 (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers). An FDG PET/CT scan should only be done (before biopsy) if other tests do not reveal a primary. HPV16 and EBV testing are recommended for squamous cell or undifferentiated histology.[528,562-565] HPV testing can be useful in workup and management of cancers of the neck of unknown primary.[566] 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.[345]

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 (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers). 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 extranodal extension, N2 or N3 without extranodal extension, or extranodal extension) (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers).

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 a neck dissection (preferred for patients with a single upper cervical lymph node ≤3 cm) followed by RT, systemic therapy/RT, or observation (only for patients with N1 disease without extranodal extension). The following options are also recommended: 1) chemoradiation for those with N2 or greater disease (category 2B); 2) primary RT for those with a single involved node ≤3 cm (category 2B); or 3) induction chemotherapy for patients with N2-3 disease (category 3) followed by chemoradiation or RT (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers). A neck dissection may be recommended after treatment with RT and/or systemic therapy, depending on the clinical response.

After a neck dissection, recommendations vary depending on the amount of nodal disease and the presence or absence of extranodal

extension. For N1 disease without extranodal extension, 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 extranodal extension (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers). For extranodal extension, concurrent chemoradiation is a category 1 recommendation; RT alone is an option (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers).[111,112] Note that the *Principles of Radiation Therapy* were extensively revised for this site (see *Occult Primary* in the NCCN Guidelines for Head and Neck Cancers; see also *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.[567] 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 cell carcinoma. The primary diagnosis of squamous cell carcinoma of the parotid gland is rare; however, the parotid gland is a frequent site of metastasis from skin cancer.[568] 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 (8th edition) (see Table 7).[39]

Treatment

The major therapeutic approach for salivary gland tumors is adequate and appropriate surgical resection.[569-572] Surgical intervention requires careful planning and execution, particularly in parotid tumor surgery because the facial nerve is in the gland. The gland should be preserved if the nerve is not directly involved by the tumor. Most parotid gland tumors are located in the superficial lobe. If the facial nerve is functioning preoperatively, the nerve can be preserved in most patients.[573] 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.

The panel recommends photon, photon/electron, or highly conformal RT for definitive radiation treatment. Pooled analyses of several studies showed better local control of advanced disease with neutron therapy, relative to photo therapy.[574,575] However, risk of late effects with neutron therapy is high and tends to increase over time, with estimates as high as 20% at 9 years.[575,576] The panel no longer recommends neutron therapy as a general solution for salivary gland cancers due to the diminishing demand, concerns regarding the methodologic robustness of available randomized trial data, and closure of all but one center in the United States. The panel recognizes the potential clinical value of neutron therapy for select patients, particularly those with unresectable disease meeting the RTOG-MRC clinical trial criteria.[575]

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 (see the NCCN Guidelines for *Salivary Gland Tumors*).[569,571,577] RT is also used in an adjuvant setting for tumors with other adverse features (eg, intermediate, high grade, T3-4 tumors);[570] systemic therapy/RT (category 2B) can also be considered (see the NCCN Guidelines for *Salivary Gland Tumors*).[578] Efficacy data for systemic therapy/RT for patients with advanced salivary gland tumors that have been resected are limited. Extensive safety data are available and may be extrapolated from the management of squamous cell H&N cancers, with some NCCN Member Institutions using platinum-based regimens for these patients. 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. Clinical trials are ongoing in this area (eg, NCT01220583, NCT02776163).

Systemic therapy 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.[579-586] Although targeted therapy is associated with stable disease, it is minimally active and is generally not recommended outside of clinical trials.[583,587] However, a significant number of advanced salivary gland tumors with distant metastases are androgen receptor-positive (AR+).[588-592] Therefore, the panel recommends that patients with tumors that are AR+ receive androgen receptor therapy (eg, leuprolide, bicalutamide).[592-594] HER2 positivity has also been found in some advanced salivary gland tumors.[590,592,595] It is recommended that these patients receive trastuzumab,[592,596] but this is a category 2B recommendation based on less consensus among the panel. AR and HER2 status should be checked in patients with distant metastases. Panel recommendations regarding targeted therapy for salivary gland tumors are based on single-institution studies and database analyses, since salivary gland tumors are rare.

Follow-up

Recommendations for surveillance are in the algorithm (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers).

Mucosal Melanoma of the Head and Neck

MM is a rare but highly aggressive neoplasm with a poor prognosis.[597,598] It mainly occurs throughout the upper aerodigestive tract.[599] Most MM (70%–80%) occurs in the nasal cavity or paranasal sinus region, and most of the remainder develops in the oral cavity.[600] The incidence of nasal cavity MM appears to be increasing.[597] Sinonasal MM is typically confined to the primary site at presentation.[601] Oral cavity MM more frequently presents with clinically apparent lymph node metastasis.[602] No etiologic risk factors are yet apparent.

Workup and Staging

Workup for MM should include clinical examination and CT and/or MRI with contrast for paranasal sinus disease and appropriate imaging for other mucosal sites. FDG PET/CT or chest/abdomen/pelvic CT and brain MRI may be considered to define distant disease in more advanced situations. The AJCC Cancer Staging Manual (8th edition) includes a staging system for MM (see Table 8).[39] 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.[603] Neck dissection with postoperative radiation is recommended for clinical nodal disease.[604,605] Adjuvant radiation appears effective in improving local control and survival in most case series.[606-608] Postoperative radiation is clearly indicated in more advanced cases.[609] 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.

Radiation Therapy

The role of RT in MM has not been evaluated in prospective trials. However, 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).[610] Retrospective studies in MM have shown local recurrence to be common after surgery alone.[611] After using postoperative radiation, lower rates of local and neck recurrence have been seen in historical comparison series.[608,612-615] Reasonable local control outcomes using RT alone in unresectable or medically inoperable cases have been reported in small cohort series of MMs.[616-618]

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 (see the NCCN Guidelines for *Mucosal Melanoma*). 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 (see the NCCN Guidelines for *Mucosal Melanoma*).

RT is often recommended in the postoperative management of MMs. Indications for postoperative radiation to the neck are generally extrapolated from cutaneous melanoma. 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.[610] Only 20 patients relapsed who received RT, whereas 34 patients relapsed who received observation only (P = .04). However, no significant differences in OS were reported.

Considering this trial and retrospective studies in MM, the NCCN Panel recommends postoperative RT for the following high-risk features: extranodal extension, 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.[619,620] 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.[610] 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. The following schedules may also be used: 1) 48 to 50 Gy (2.4–3 Gy/fraction); or 2) 30 to 36 Gy (6 Gy/fraction).[610,612,620]

IMRT may be very useful in helping to achieve homogenous dose distributions and to spare critical organs, especially in paranasal sinus sites.[192,497,621] 3D-CRT may also be used. 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.[621] Care should be taken when RT is used in combination with BRAF inhibitors, as concurrent use has been found to be associated with grade ≥3 dermatologic reactions, and potentially lethal hemorrhaging in the liver, lung, and brain have all been reported.[622]

Systemic Therapy

Systemic therapy used for cutaneous melanoma (eg, interleukin-2) is recommended for MM (see *Systemic Therapy for Metastatic or Unresectable Disease* in the NCCN Guidelines for [cutaneous] Melanoma, available at www.NCCN.org).[601,623] Interferon and interleukin have been used to treat MM.[623,624] Data suggest that *c-KIT* inhibitors (eg, imatinib) may be useful in selected patients with metastatic MM and specific mutations.[625-628] Therefore, *c-KIT* inhibitors are reasonable to use in patients with MM who have *c-KIT* mutations (ie, exon 11 or 13 mutations).[623,629,630] 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.[623,630,631]

Follow-up

Recommendations for surveillance are provided in the algorithm (see *Follow-up Recommendations* in the NCCN Guidelines for Head and Neck Cancers). Note that physical examination for MM should include endoscopic inspection for paranasal sinus disease.

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Figure 1: Anatomic Sites and Subsites of the Head and Neck

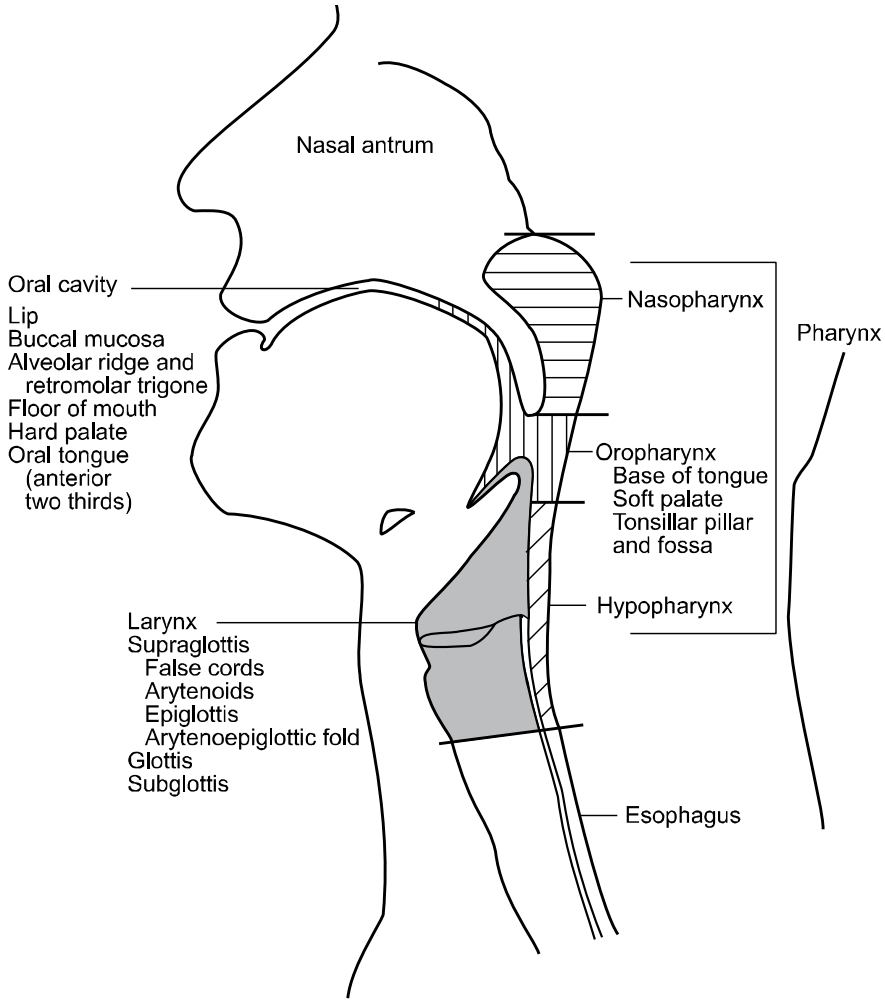

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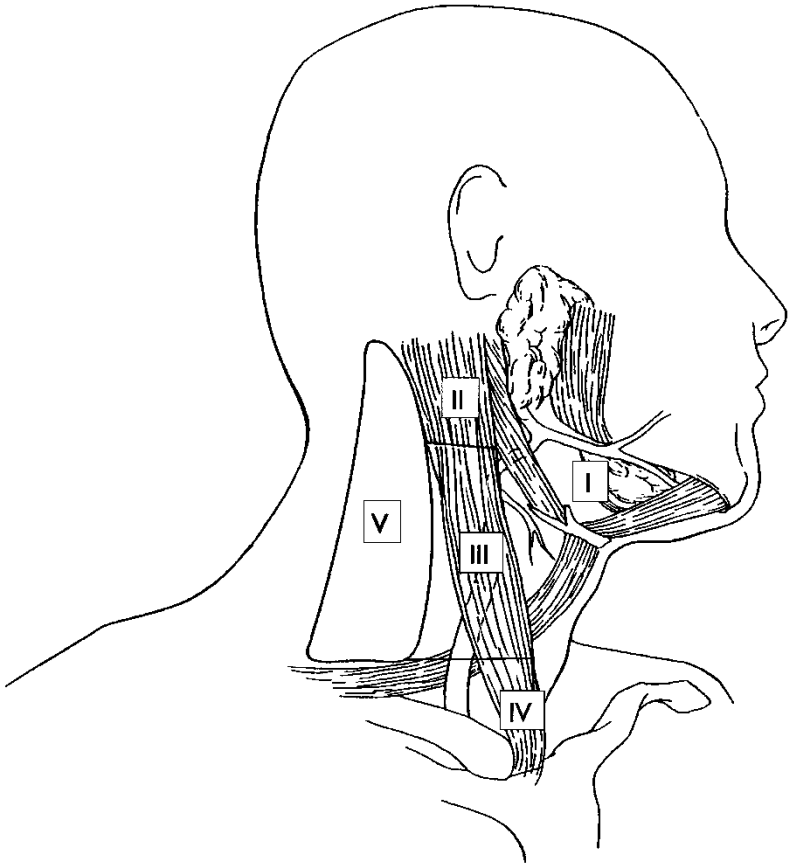
Figure 2: Level Designation for Cervical Lymphatics in the Right Neck



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