National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Head and Neck Cancers

V.2.2010

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Print the Head and Neck Cancers Guideline

For help using these documents, please click here

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

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

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

See NCCN Categories of Evidence and Consensus

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2010.

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Summary of the Guidelines updates

The 2.2010 version of the Head and Neck Cancers guidelines represents the addition of the Discussion text correspondent to the changes in the algorithm (MS-1).

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

Global Changes

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

TEAM-1

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

Cancer of the Lip

LIP-1

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

LIP-2

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

LIP-3

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

LIP-A

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

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Summary of the Guidelines updates

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

Cancer of the Oral Cavity

OR-2

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

OR-A

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

Cancer of the Oropharynx

ORPH-1

- Workup: The third bullet was clarified as "Tumor HPV testing suggested".
- Footnotes "a" and "b" are new to the page.

ORPH-2

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

ORPH-3

- For T3-4a, N0-1 disease:
  - Surgery was clarified as "for primary and neck".

ORPH-3---continued

- "Induction chemotherapy followed by chemo/RT (category 3)" changed to "Induction chemotherapy followed by RT or chemo/RT (category 3)".

ORPH-4

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

ORPH-A

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

Cancer of the Hypopharynx

HYPO-1

- Clinical Staging: "T Stage not requiring total laryngectomy" changed to "Not requiring total laryngectomy." "Resectable advanced cancer requiring total laryngectomy" changed to "Advanced cancer requiring total laryngectomy."

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Summary of the Guidelines updates

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

Cancer of the Hypopharynx---continued

HYPO-3

- Treatment of Primary and Neck: Induction chemotherapy x 2 cycles (category 1), changed to "Induction chemotherapy (category 1)."
- Footnote "f" that states, "In randomized clinical trials, assessment of response has been done after 2 or 3 cycles", is new to the algorithm. (Also for HYPO-5, GLOT-5, and SUPRA-7)

HYPO-4

- Primary site: Complete Response: After Definitive RT (category 1), "Consider chemo/RT (category 2B)" was added as an option.
- After PR, "Induction chemotherapy 3rd cycle" was removed.
- Footnote "d": "Selected pT1-T2, N0-N1" was added as an adverse feature.

HYPO-5

- "x 3 cycles" was removed from Induction chemotherapy.
- After Primary site: "CR or PR: Chemo/RT" changed to "For CR: RT or consider chemo/RT; For PR: Chemo/RT".
- Primary site < PR or progression in neck pathway: After salvage surgery + neck dissection as indicated, "RT or Chemo/RT" were added as treatment options.

HYPO-A

- Definitive RT:
  - Under Primary and gross adenopathy, "Conventional fractionation 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday)" was added
  - Altered fractionation dose for 6 fractions/week accelerated; changed from "70 Gy to gross disease, ≥ 50 Gy to subclinical disease" to "66-74 Gy to gross disease and 44-64 Gy to subclinical disease."
  - Neck; Uninvolved nodal stations: Changed from "≥ 50 Gy (2.0 Gy/day)" to "44-64 Gy (1.6-2.0 Gy/fraction)." (Also for Postoperative RT)
- Postoperative RT:
  - Neck; Involved nodal stations: Changed from "≥ 60 Gy" to "60-66 Gy."
- Footnote "2": "Particular attention to speech and swallowing needs during therapy," is new to the page.

Cancer of the Nasopharynx

NASO-1

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

NASO-2

- "Induction chemotherapy followed by Chemo/RT (category 3)" was added as an option for T1, N1-3; T2-T4, Any N disease.
- "Chemo/RT" was added as an option after complete response for Any T, Any N, M1 disease.

NASO-A

- Primary and gross adenopathy: "≥ 70 Gy" changed to "66-70 Gy".
- Neck; Uninvolved nodal stations: Changed from "≥ 50 Gy (2.0 Gy/day)" to "44-64 Gy (1.6-2.0 Gy/fraction)".

Cancer of the Glottic Larynx

GLOT-1

- "Resectable" was removed as a bullet from the third and fourth pathways.

GLOT-2

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

GLOT-3

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

GLOT-4

- "Induction chemotherapy x 3 cycles (category 2B)" changed to "Induction chemotherapy (category 3)."

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Summary of the Guidelines updates

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

Cancer of the Glottic Larynx---continued.

GLOT-5

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

GLOT-6

- The bottom pathway changed to "Selected T4a patients who decline surgery".

GLOT-A

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

Cancer of the Supraglottic Larynx

- The algorithms were revised including page deletions and updated pagination.

SUPRA-1

- Clinical Staging: In the second pathway: "T4a, N0" was removed as a bullet and the third pathway changed from "T4, N0" to "T4a, N0".

SUPRA-2

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

SUPRA-3

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

SUPRA-4

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

SUPRA-5

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

SUPRA-7

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

SUPRA-8

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

SUPRA-A

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

Ethmoid Sinus Tumors

ETHM-1

- A new column entitled "Clinical Presentation" was added with pathway "Unresected mass or Incompletely resected mass".
- The "Diagnosed with incomplete excision" pathway was removed.

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Summary of the Guidelines updates

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

Ethmoid Sinus Tumors

ETHM-1---continued

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

ETHM-2

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

Maxillary Sinus Tumors

MAXI-1

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

MAXI-2

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

MAXI-A

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

MAXI-A---continued

- Definitive RT:
  - Altered fractionation dose changed from "6 fractions/week accelerated; 70 Gy to gross disease, ≥ 50 Gy to subclinical" to "…66-74 Gy to gross disease, 44-64 Gy to subclinical disease".
  - RT dosing for Neck; Uninvolved nodal stations changed from "≥ 50 Gy (2.0 Gy/day)" to "44-64 Gy (1.6-2.0 Gy/fraction)". (Also for Postoperative RT)
- Postoperative RT:
  - Primary: "≥ 60 Gy" changed to "60-66 Gy".
  - Neck; Involved nodal stations changed from "≥ 60 Gy" to "60-66 Gy".

Advanced Head and Neck Cancer

ADV-1 (Very Advanced Head and Neck Cancer)

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

ADV-2 (Recurrent/Persistent Disease)

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

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Summary of the Guidelines updates

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

Advanced Head and Neck Cancer---continued

ADV-A

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

Occult Primary

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

OCC-1

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

OCC-2

- Third column: Adenocarcinoma was clarified as "of neck node".
- The "Poorly differentiated…" and "Squamous cell carcinoma…" pathways were combined.

OCC-3

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

OCC-4

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

OCC-5

- Second column: "Extracapsular spread or N2, N3" changed to "N2, N3 without extracapsular spread".

OCC-6

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

OCC-A

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

Salivary Gland Tumors

SALI-1, SALI-2, SALI-3, SALI-4

- The entire salivary gland tumors algorithm was revised.

SALI-A

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

Mucosal Melanoma

MM-1, MM-2, MM-3, MM-4, MM-A

- This is a new algorithm that provides workup, treatment, follow-up, and radiation recommendations for mucosal melanoma.

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Summary of the Guidelines updates

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

FOLL-A Follow-up Recommendations

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

SURG-A Principles of Surgery

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

RAD-A Radiation Techniques

- **Intensity-Modulated Radiotherapy (IMRT): "IMRT has been shown to be particularly useful in reducing long-term toxicity…" changed to "IMRT has been shown to be useful in reducing long-term toxicity…"**

CHEM-A Principles of Systemic Therapy

Squamous Cell Cancers: Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic larynx, Supraglottic larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- **Primary Systemic Therapy + concurrent RT**
  - **Cisplatin alone (preferred) changed from category 2A to "category 1".**
  - **Cetuximab changed from category 2A to "category 1".**
  - **Carboplatin/taxol (category 2B) was added.**
- **Postoperative Chemoradiation**
  - **Cisplatin alone was designated category 1 for high risk.**
- **Induction/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU designated (category 1 if induction is chosen)**
  - **Footnote that states, "Induction chemotherapy should only be done in a tertiary setting" is new to the page.**
  - **The statement, "Following induction, agents to be used with concurrent chemoradiation typically include weekly platinums, weekly taxanes, or cetuximab" is new to the page.**

Nasopharynx

- **Chemoradiation followed by adjuvant chemotherapy**
  - **Cisplatin + RT followed by Cisplatin/5-FU changed from category 2A to "category 1".**

Recurrent, Unresectable, or Metastatic (incurable):

- **Combination therapy**
  - **"Cisplatin or carboplatin + 5-FU ± cetuximab" changed to "Cisplatin or carboplatin + 5-FU + cetuximab (category 1)."**
  - **Cisplatin + 5-FU was added.**

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MULTIDISCIPLINARY TEAM

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

- Head and neck surgery
- Radiation oncology
- Medical oncology
- Plastic and reconstructive surgery
- Specialized nursing care
- Dentistry/prosthodontics
- Physical medicine and rehabilitation
- Speech and swallowing therapy
- Clinical Social work
- Nutrition support
- Pathology (including cytopathology)
- Diagnostic radiology
- Adjunctive services
  - Neurosurgery
  - Ophthalmology
  - Psychiatry
  - Addiction Services
  - Audiology
  - Palliative care

SUPPORT AND SERVICES

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

- General medical care
- Pain and symptom management
- Nutritional support
  - Enteral feeding
  - Oral supplements
- Dental care for RT effects
- Xerostomia management
- Smoking and alcohol cessation
- Speech and swallowing therapy
- Audiology
- Tracheotomy care
- Wound management
- Depression assessment and management
- Social work and Case management
- Supportive Care
  (See NCCN Palliative Care Guideline)

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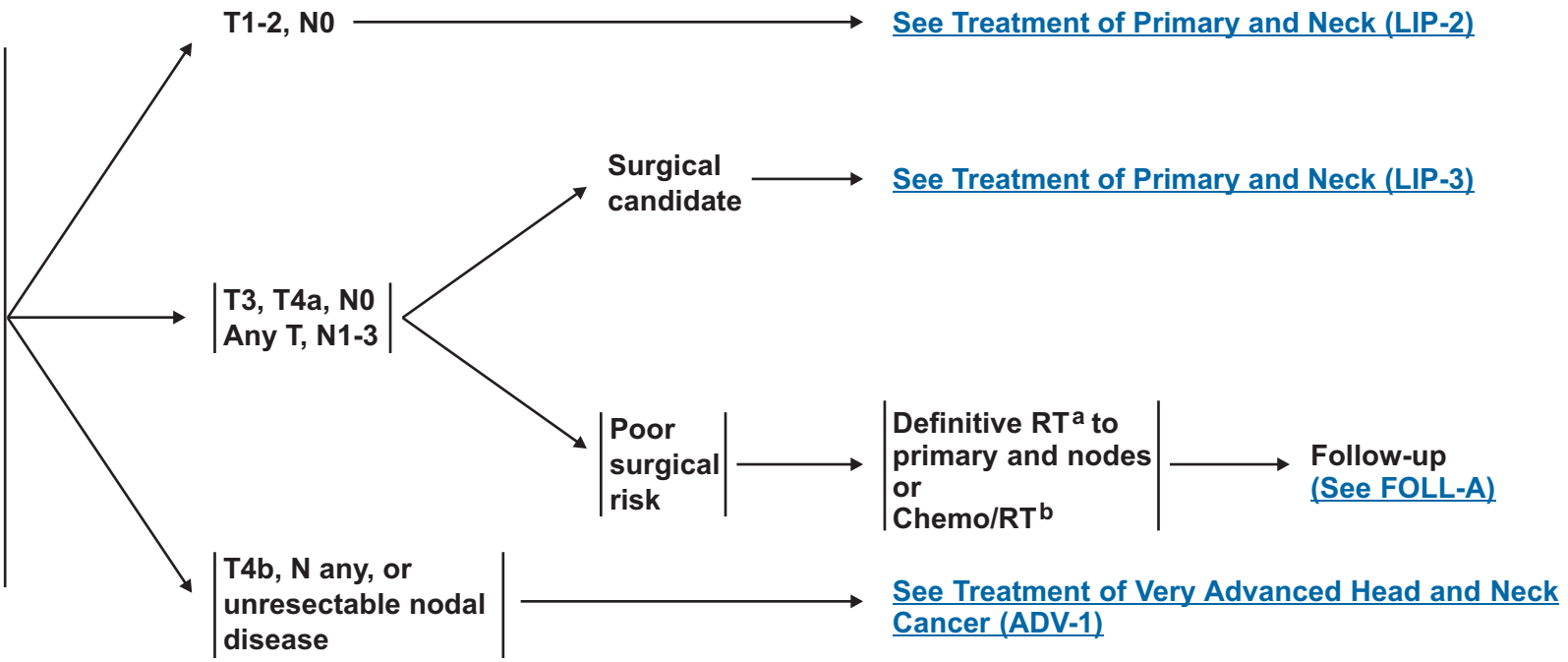
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WORKUP

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

Multidisciplinary consultation as indicated

CLINICAL STAGING

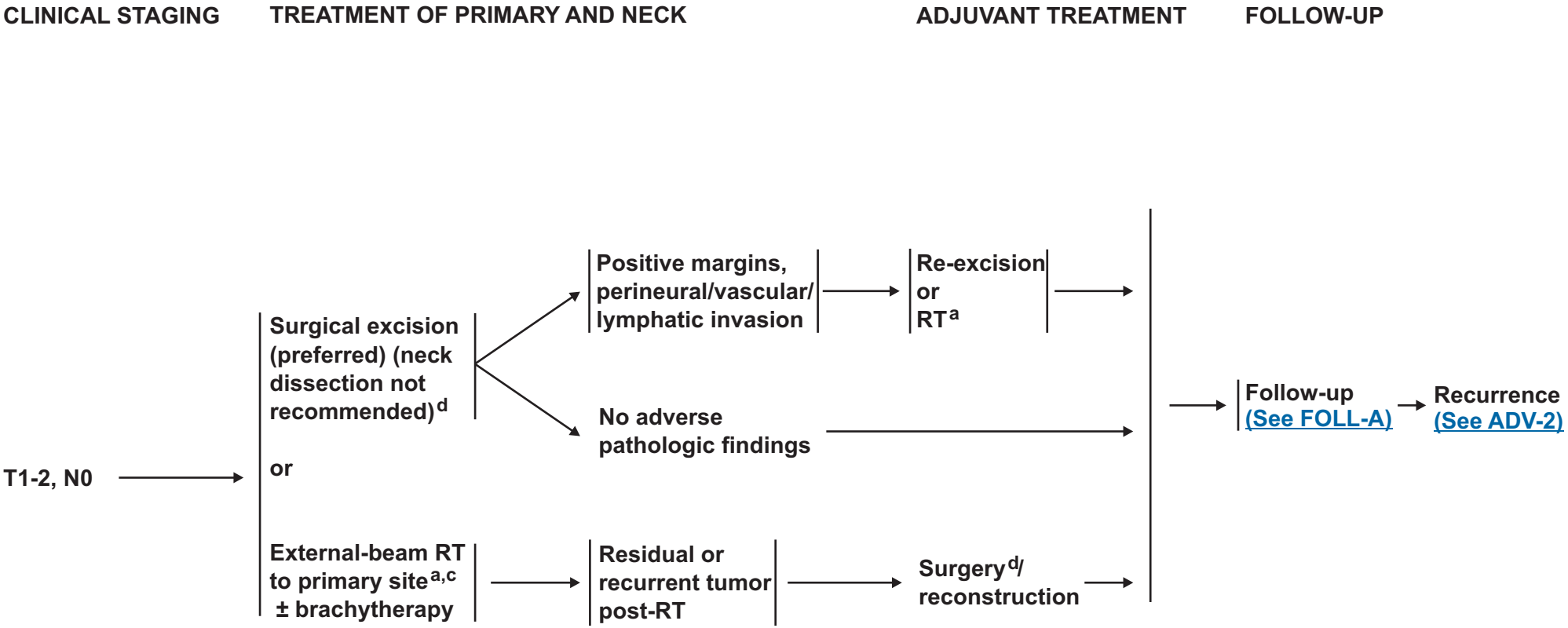


[a] See Principles of Radiation Therapy (LIP-A).
[b] See Principles of Systemic Therapy (CHEM-A).

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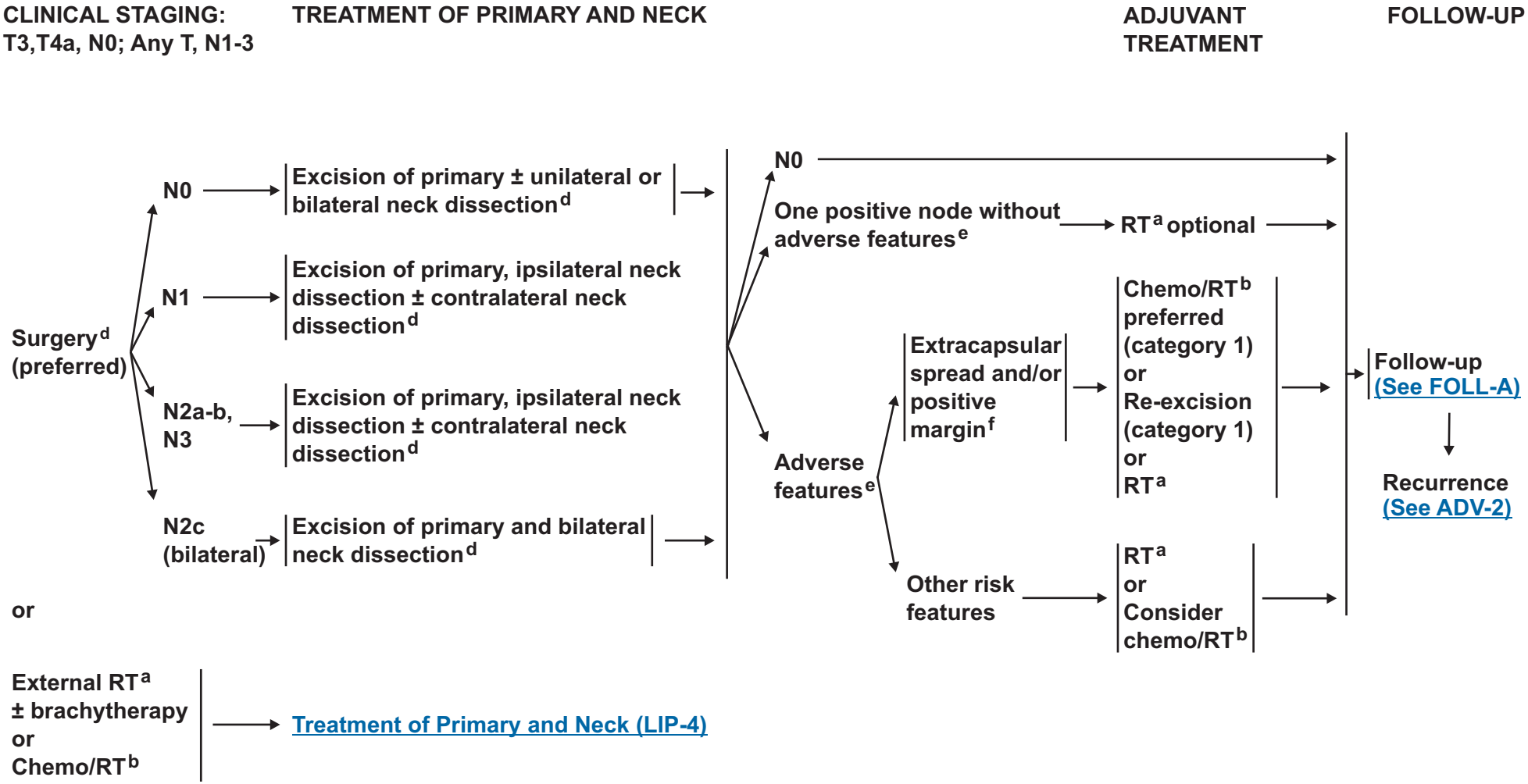


[a] See Principles of Radiation Therapy (LIP-A).
[c] No elective treatment to neck preferred for T1-2, N0.
[d] See Principles of Surgery (SURG-A).

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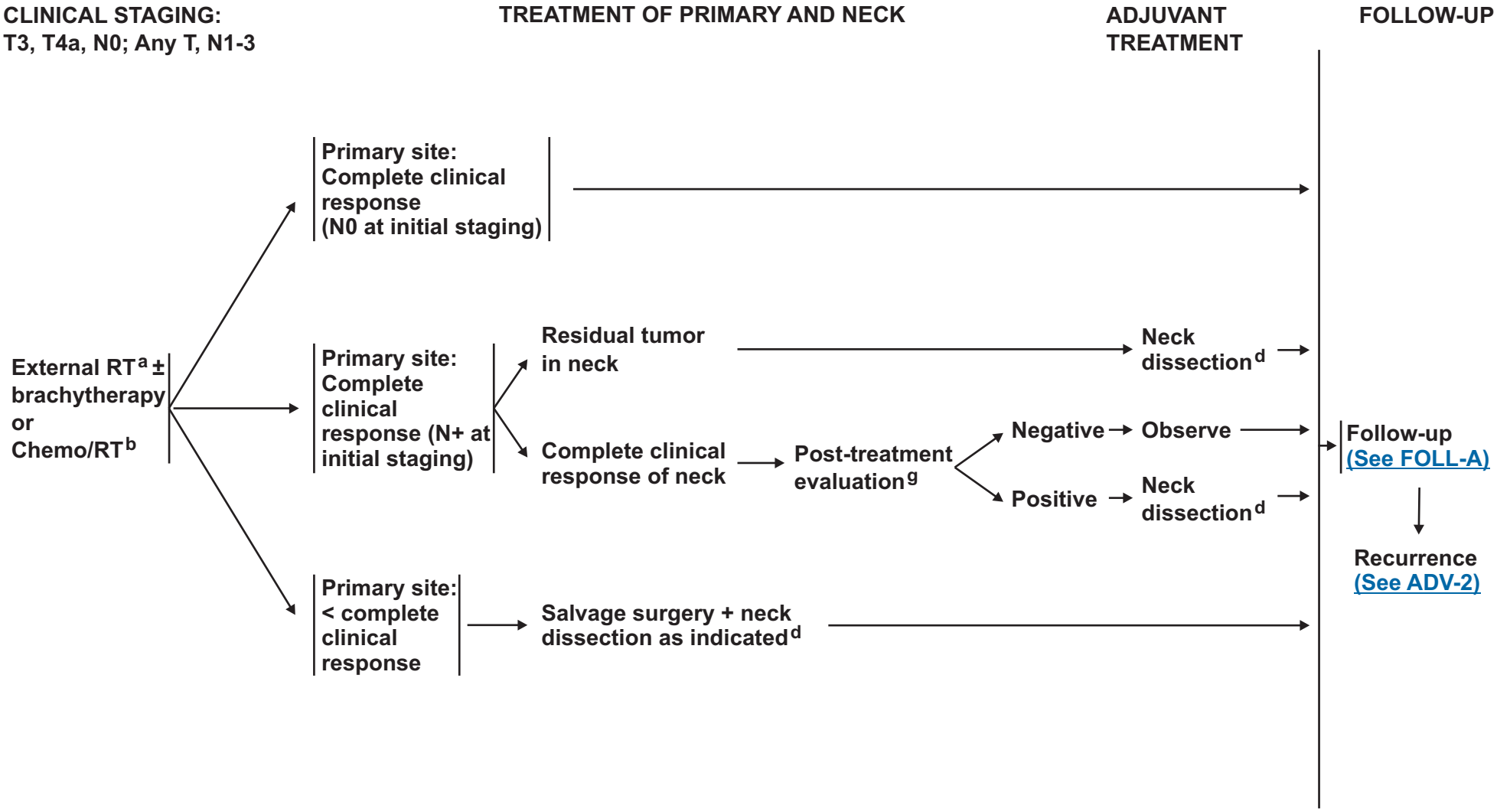
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[a] See Principles of Radiation Therapy (LIP-A).
[b] See Principles of Systemic Therapy (CHEM-A).
[d] See Principles of Surgery (SURG-A).
[e] Adverse features: extracapsular nodal spread, positive margins, multiple positive nodes or perineural/lymphatic/vascular invasion.
[f] For positive margin only, re-excise if technically feasible.

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[a] See Principles of Radiation Therapy (LIP-A).
[b] See Principles of Systemic Therapy (CHEM-A).
[d] See Principles of Surgery (SURG-A).
[g] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

- **Primary and gross adenopathy:**
  66-74 Gy (2.0 Gy/fraction)
  External-beam RT ± brachytherapy
  50-60 Gy with brachytherapy
  50-66 Gy without brachytherapy
- **Neck**
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)

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

Postoperative RT

- **Primary: ≥ 60 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Involved nodal stations:**
    60-66 Gy (2.0 Gy/fraction)
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)

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

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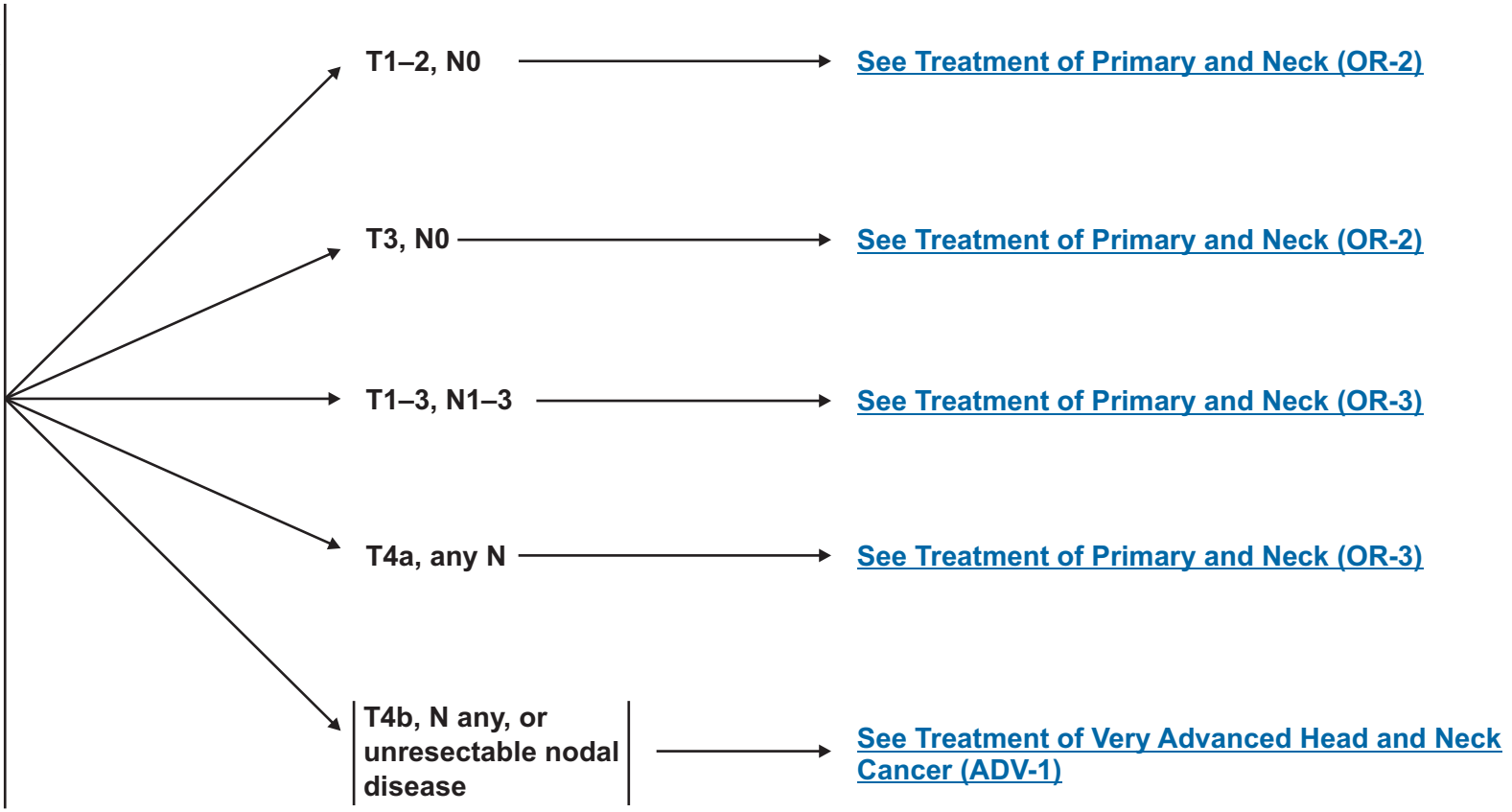
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

WORKUP

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

Multidisciplinary consultation as indicated

CLINICAL STAGING

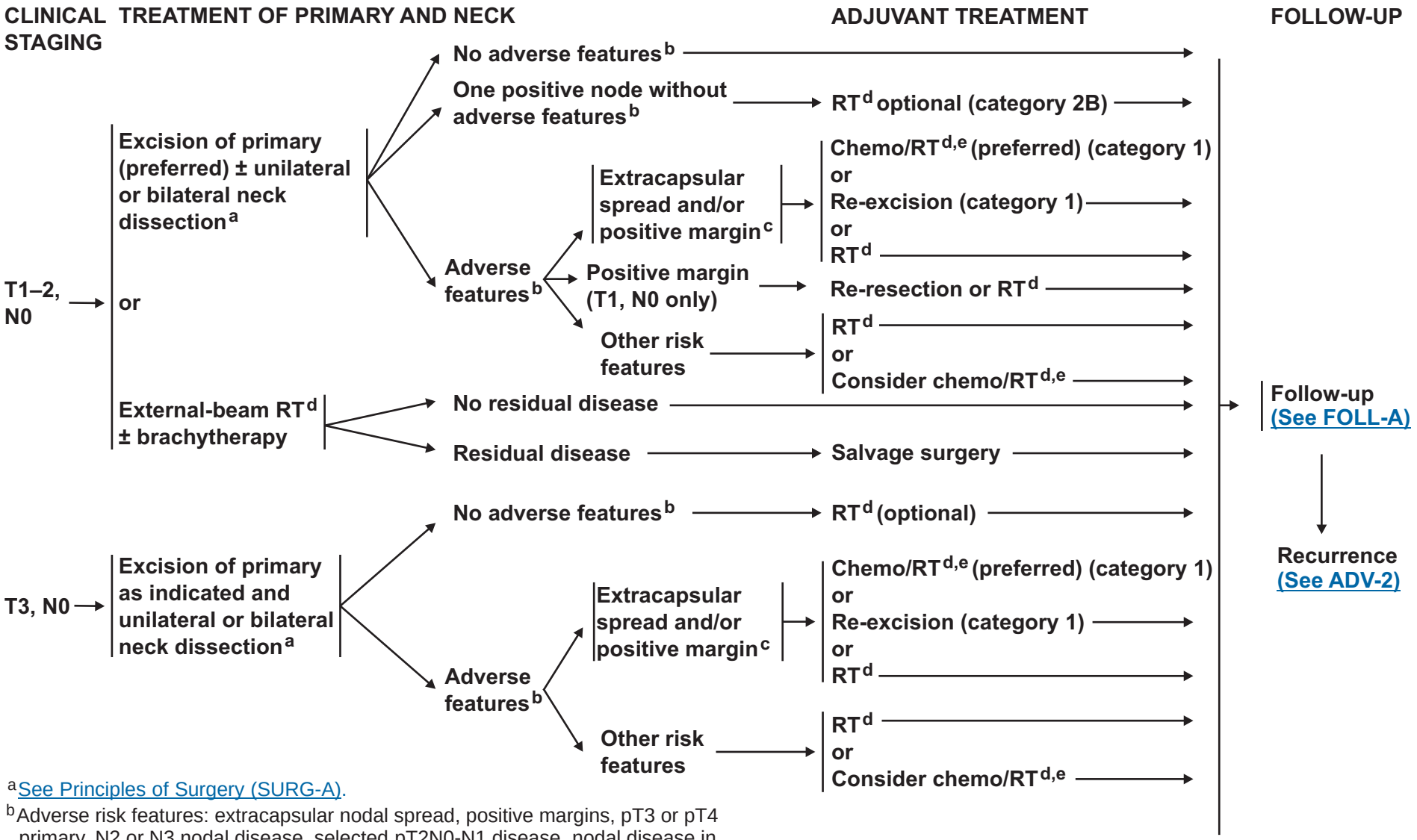


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Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



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

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

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

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

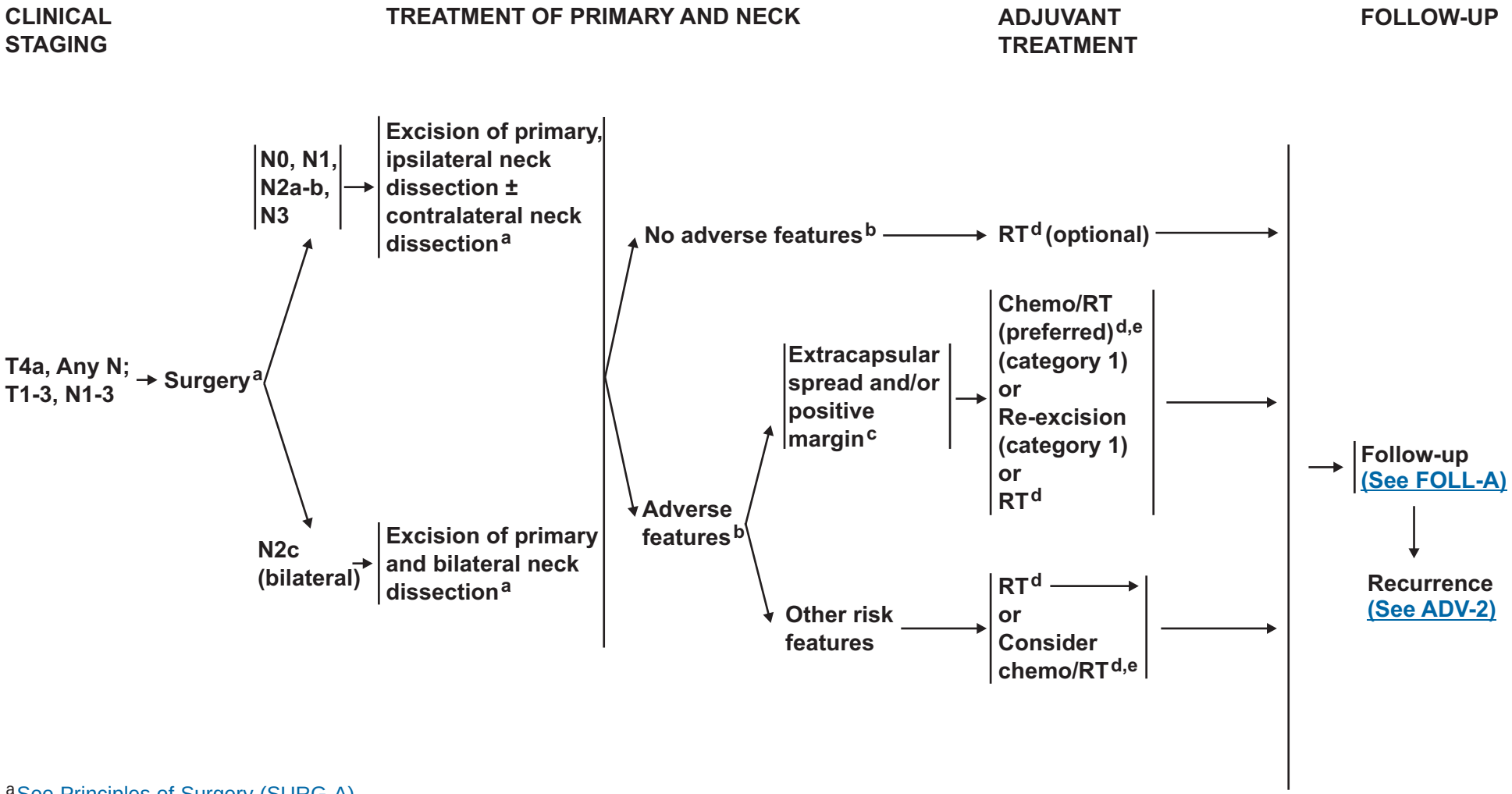
[e] See Principles of Systemic Therapy (CHEM-A).

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

[b] Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT2, N0-N1 disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

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

Postoperative RT

- **Indicated for pT3 or pT4 primary; N2 or N3 nodal disease, selected pT2, N0-N1 disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.**
- **Preferred interval between resection and postoperative RT is ≤ 6 weeks.**
- **Primary: ≥ 60 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Involved nodal stations:**
    60-66 Gy (2.0 Gy/fraction)
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative chemoradiation

- **Indicated for extracapsular nodal spread and/or positive margins[2-4]**
- **Consider for other risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.**
- **Concurrent single agent cisplatin at 100 mg/m^2 every 3 wks is recommended.**

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

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

[3] Cooper JS, Pajak TF, Forastiere AA et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350(19):1937-1944.

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

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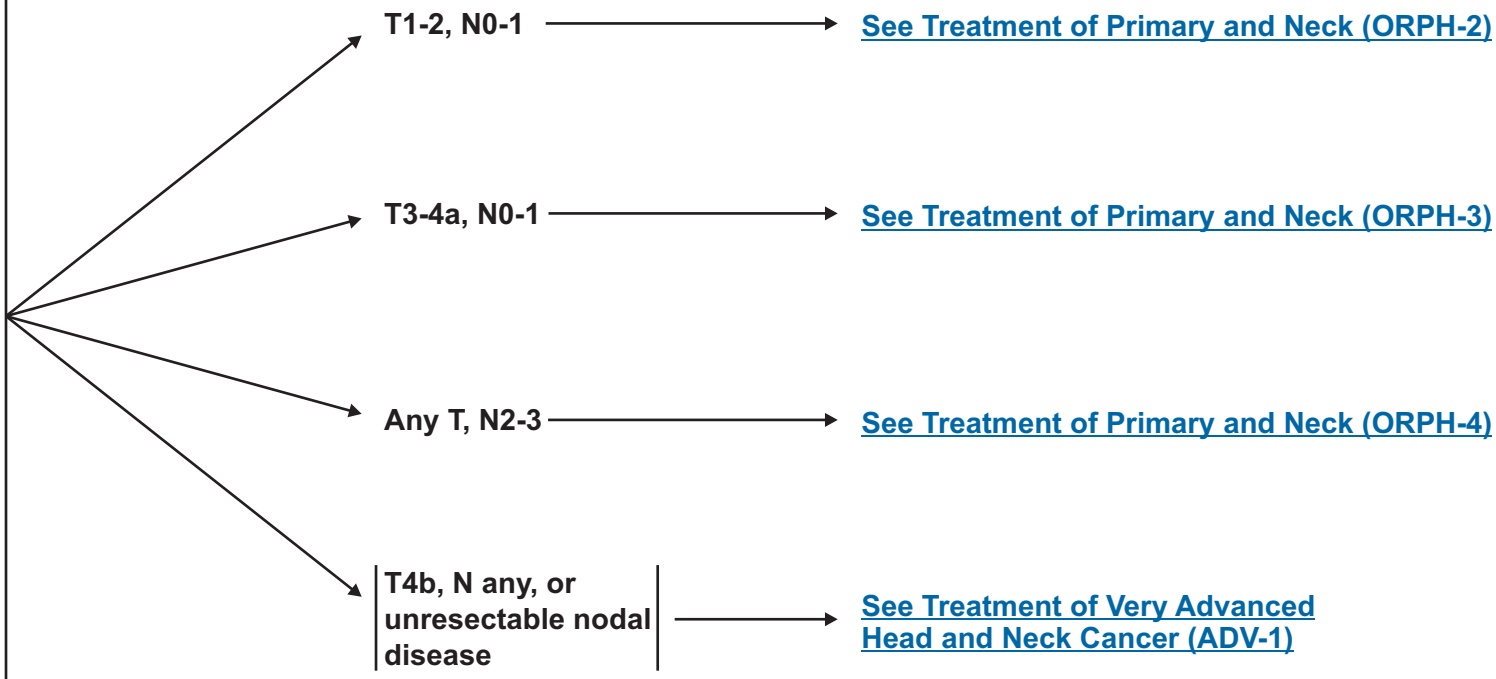
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

WORKUP

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

Multidisciplinary consultation as indicated

CLINICAL STAGING

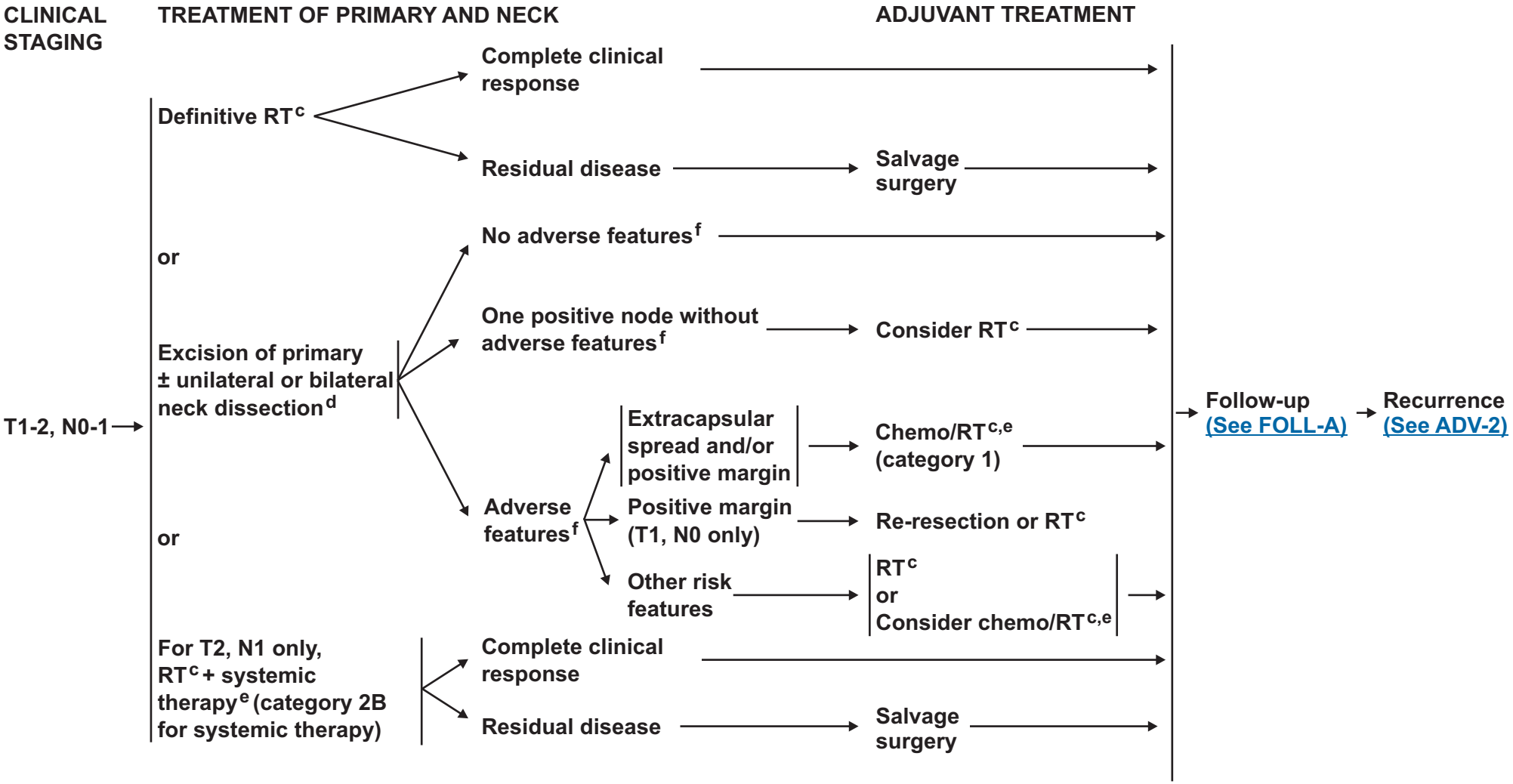


[a] Immunohistochemical staining for p16 is recommended. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.
[b] Anatomical imaging is also recommended.

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



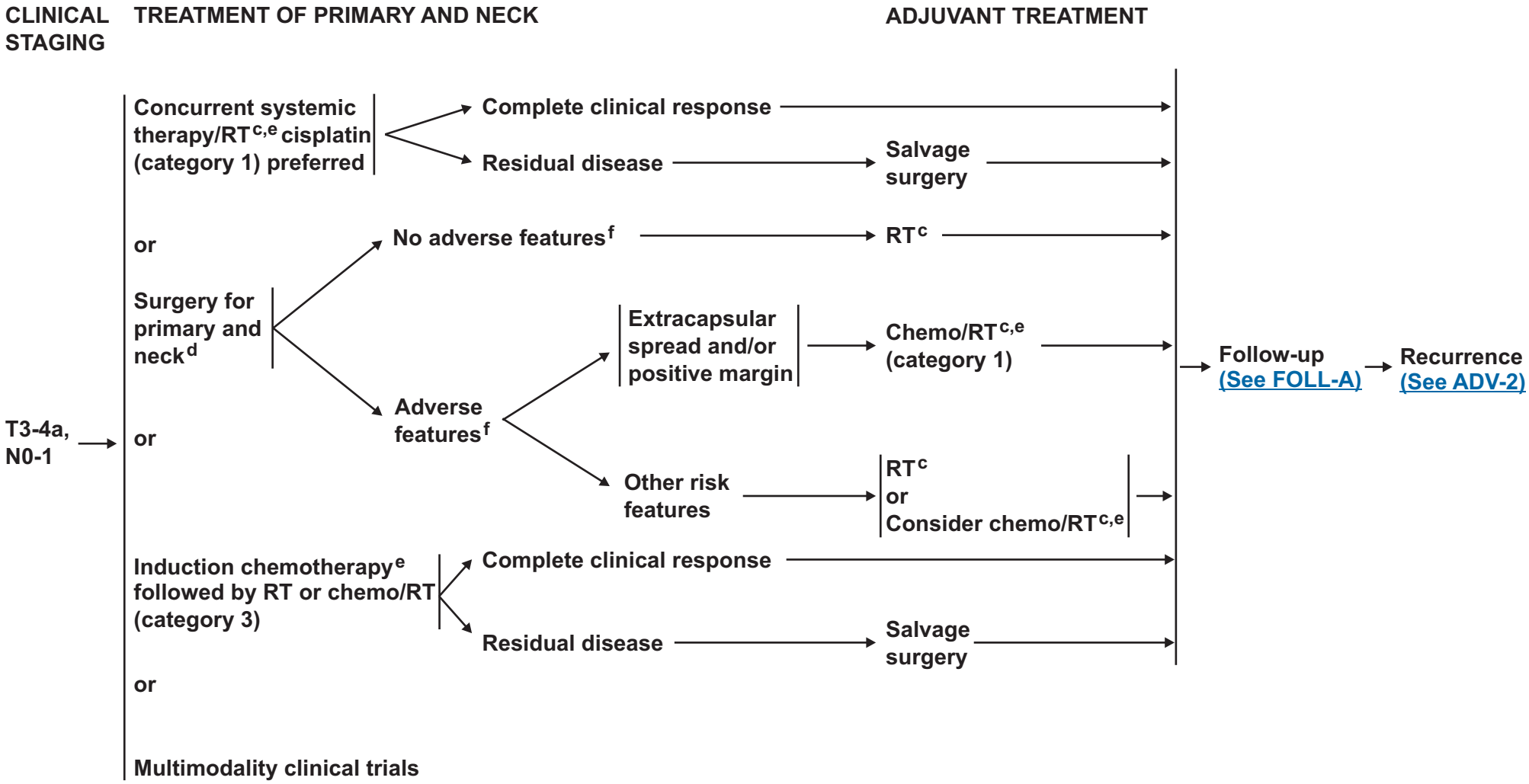
[c] See Principles of Radiation Therapy (ORPH-A).
[d] See Principles of Surgery (SURG-A).
[e] See Principles of Systemic Therapy (CHEM-A).
[f] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

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



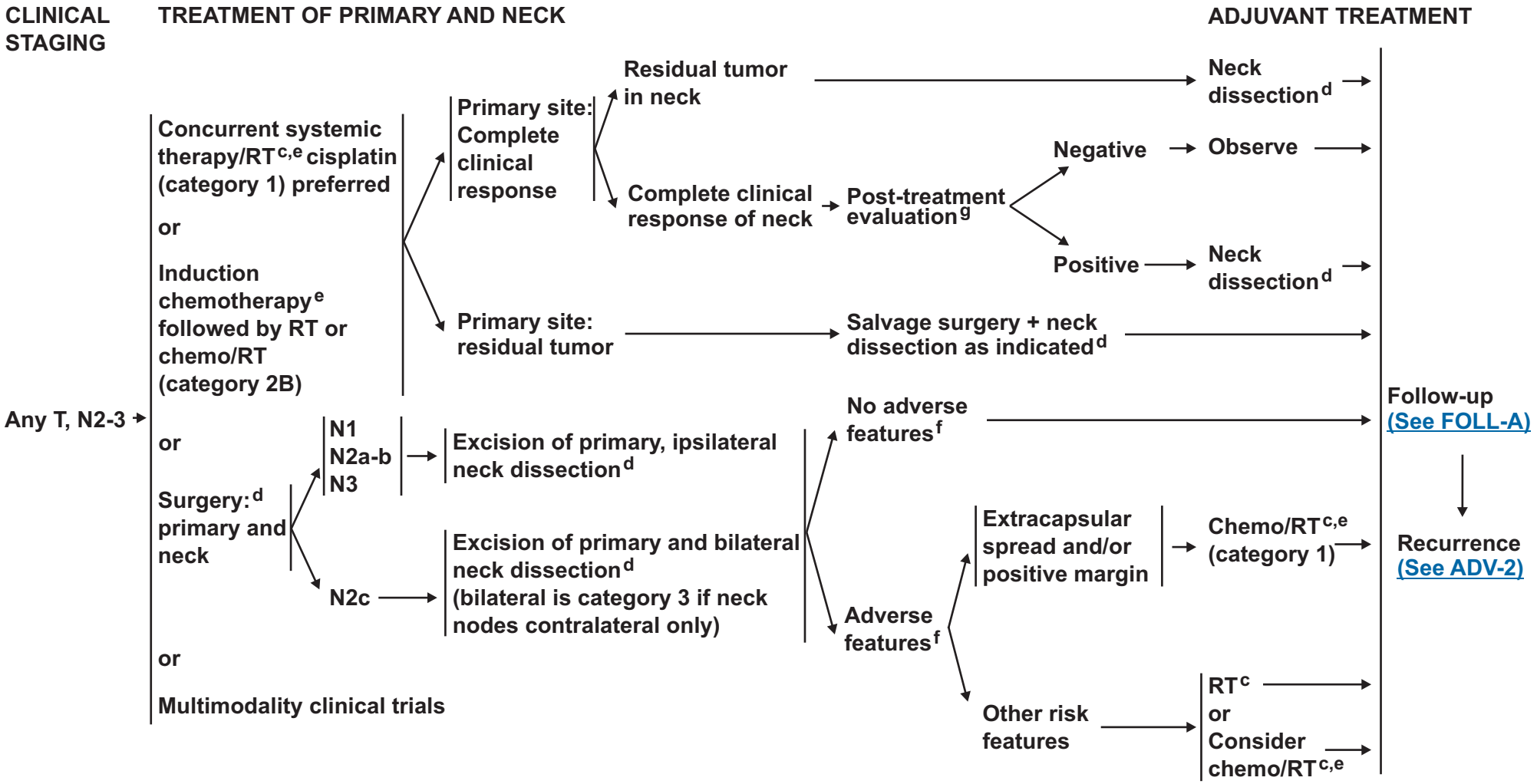
[c] See Principles of Radiation Therapy (ORPH-A).
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Base of tongue/tonsil/posterior pharyngeal wall/soft palate



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[f] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.
[g] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

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

Postoperative RT

- Indicated for pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.
- Preferred interval between resection and postoperative RT is ≤ 6 weeks.
- Primary: ≥ 60 Gy (2.0 Gy/fraction)
- Neck
  - Involved nodal stations: 60-66 Gy (2.0 Gy/fraction)
  - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

Concurrent chemoradiation

Conventional fractionation:[2]

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

Postoperative chemoradiation

- Indicated for extracapsular nodal spread and/or positive margins[3-5]
- Concurrent single agent cisplatin at 100 mg/m^2 every 3 wks x 3 doses is recommended.
- Consider for other risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

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

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

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

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

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

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

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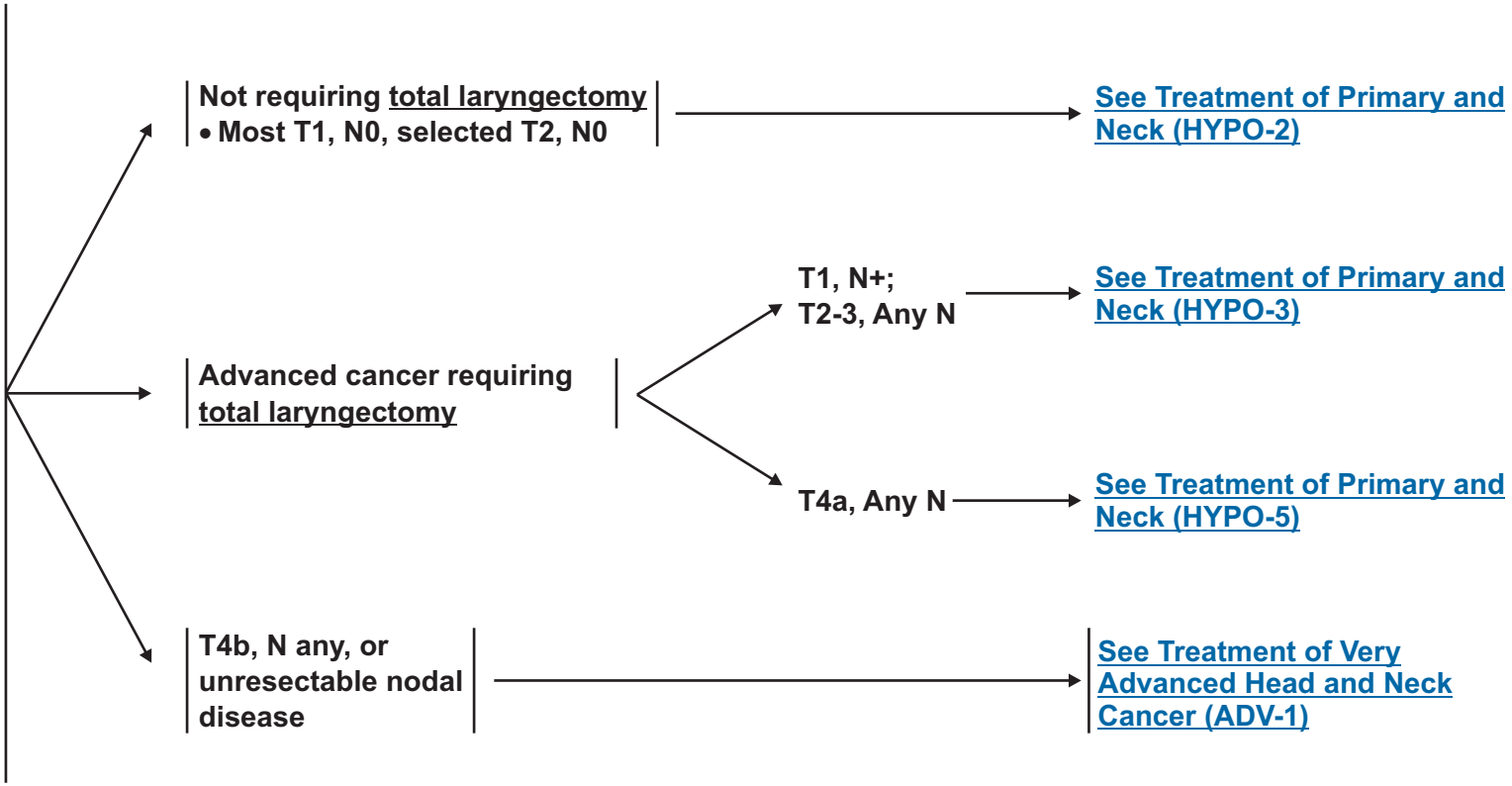
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WORKUP

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

Multidisciplinary consultation as indicated

CLINICAL STAGING

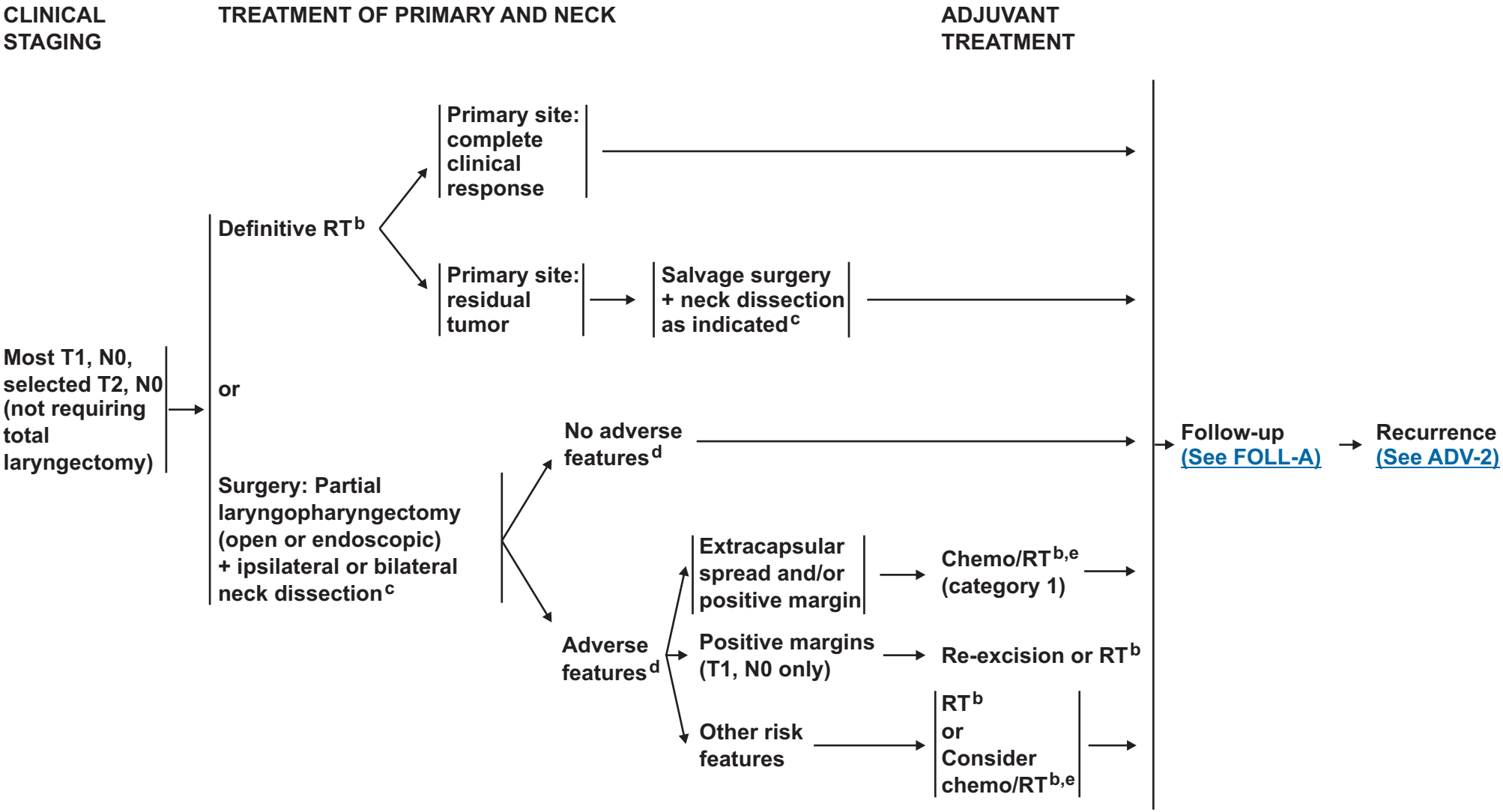


[a]Anatomical imaging is also recommended.

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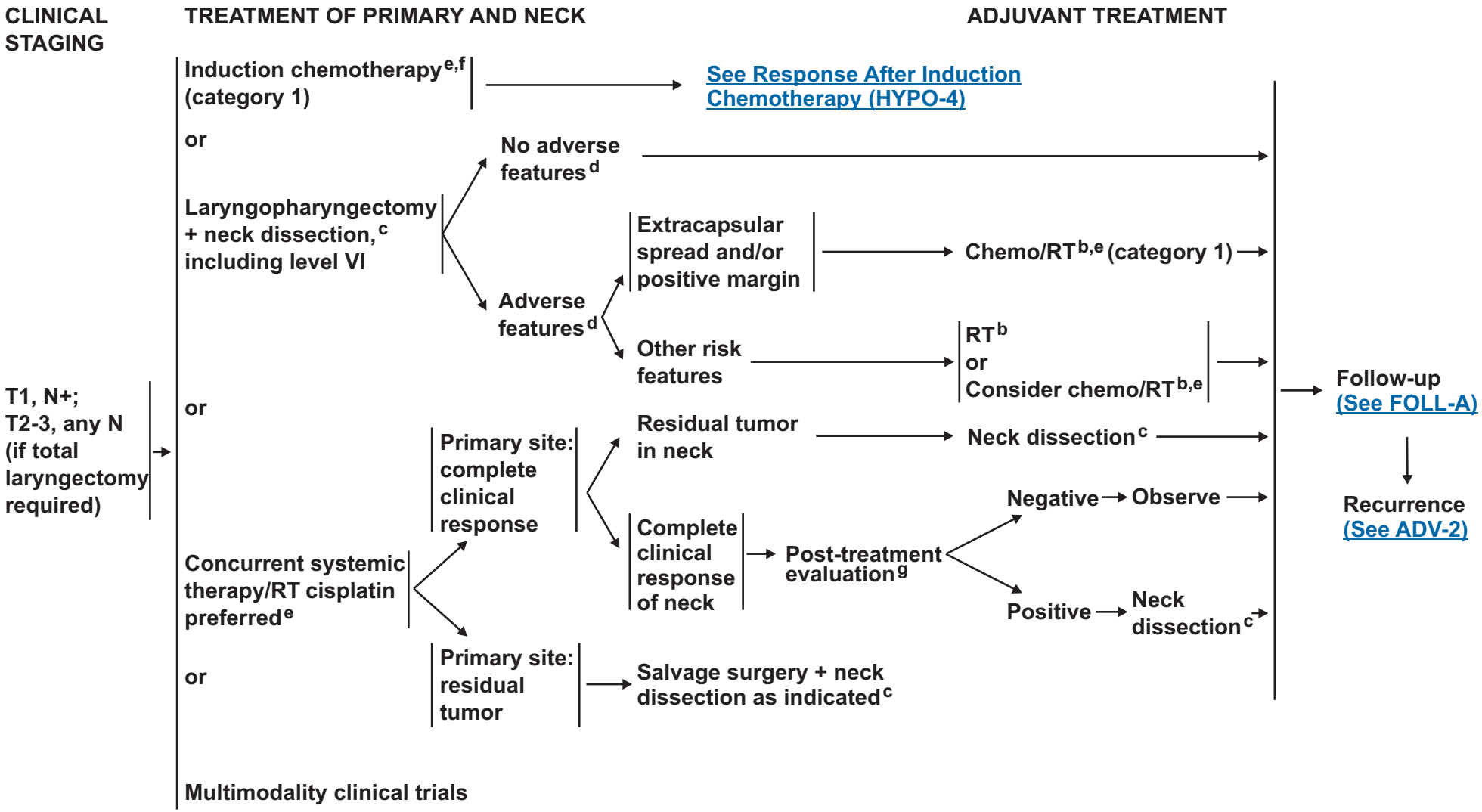


[b] See Principles of Radiation Therapy (HYPO-A).
[c] See Principles of Surgery (SURG-A).
[d] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, N0-N-1, perineural invasion, vascular embolism.
[e] See Principles of Systemic Therapy (CHEM-A).

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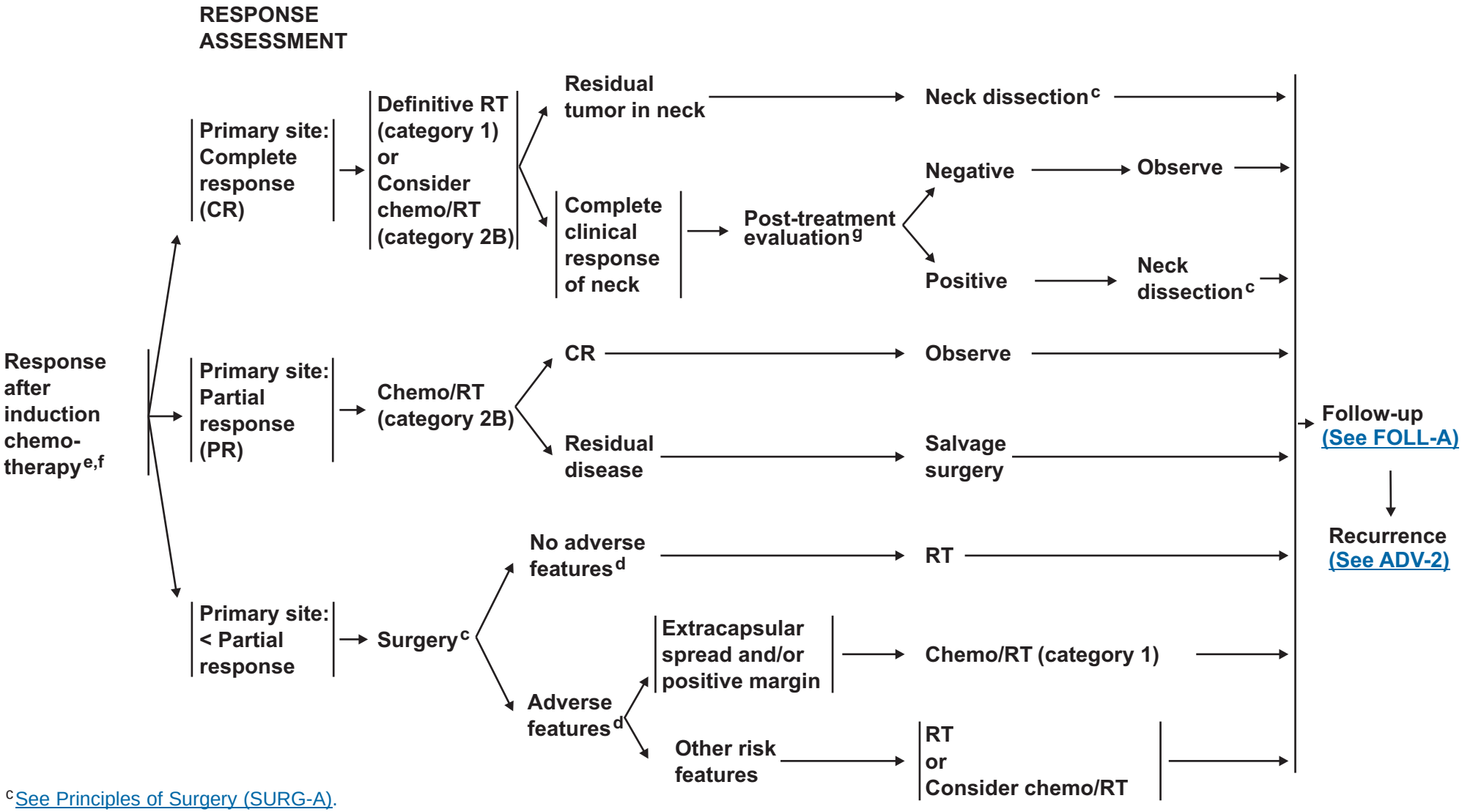
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[g] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).

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[d] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, N0-N1, perineural invasion, vascular embolism.

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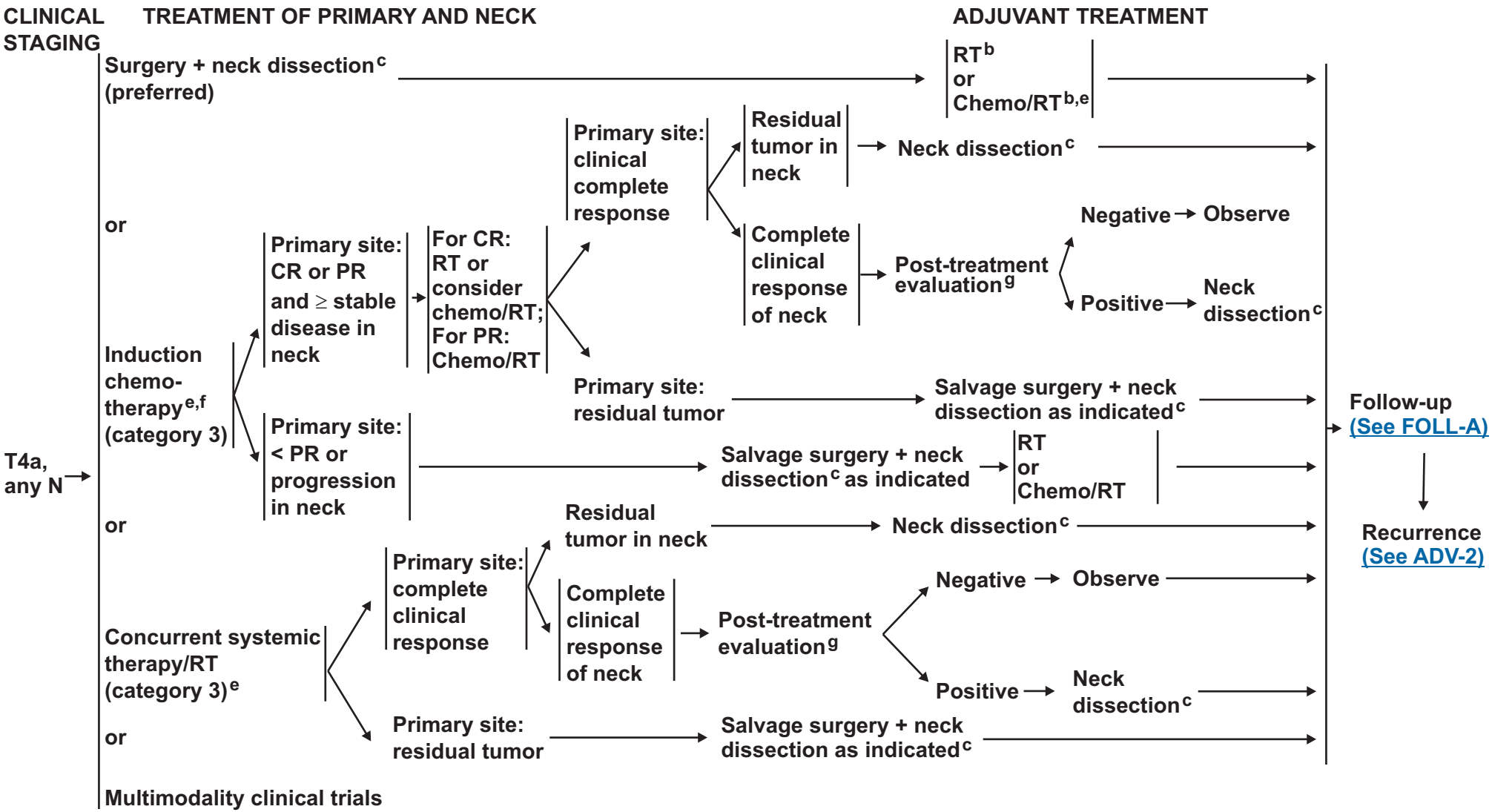
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PRINCIPLES OF RADIATION THERAPY[1,2]

Definitive RT

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

Postoperative RT

- **Indicated for pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, N0-N1, perineural invasion, vascular embolism.**
- **Preferred interval between resection and postoperative RT is ≤ 6 weeks.**
- **Primary: ≥ 60 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Involved nodal stations:**
    60-66 Gy (2.0 Gy/fraction)
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative chemoradiation

- **Indicated for extracapsular nodal spread and/or positive margins[3-5]**
- **Consider for other risk features: pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.**
- **Concurrent single agent cisplatin at 100 mg/m^2 every 3 wks is recommended.**

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

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

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

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

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

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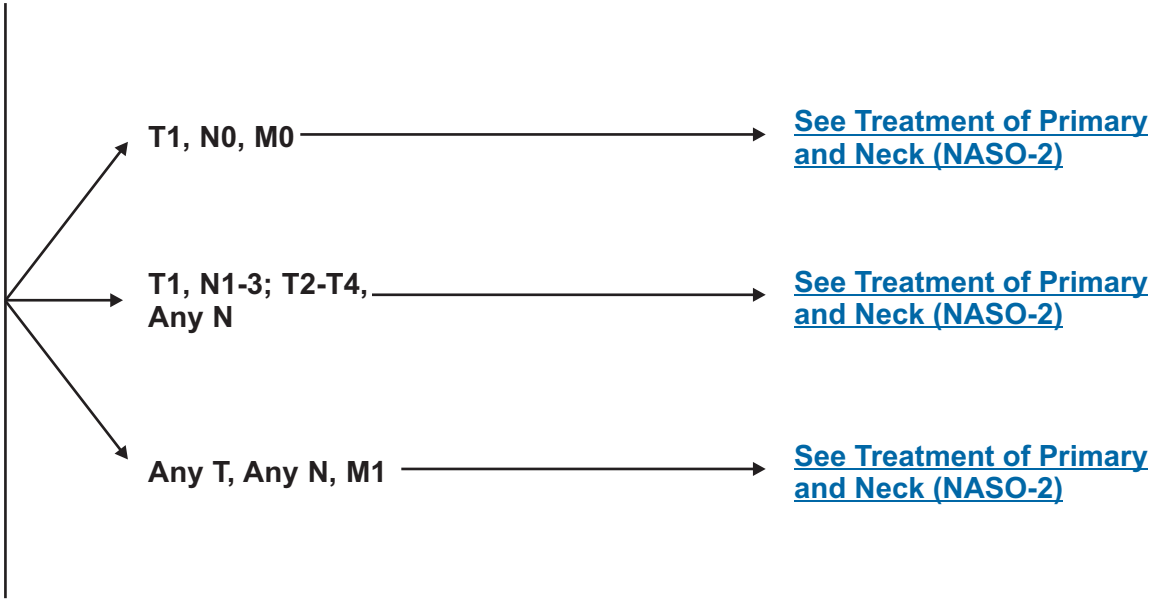
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WORKUP

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

Multidisciplinary consultation

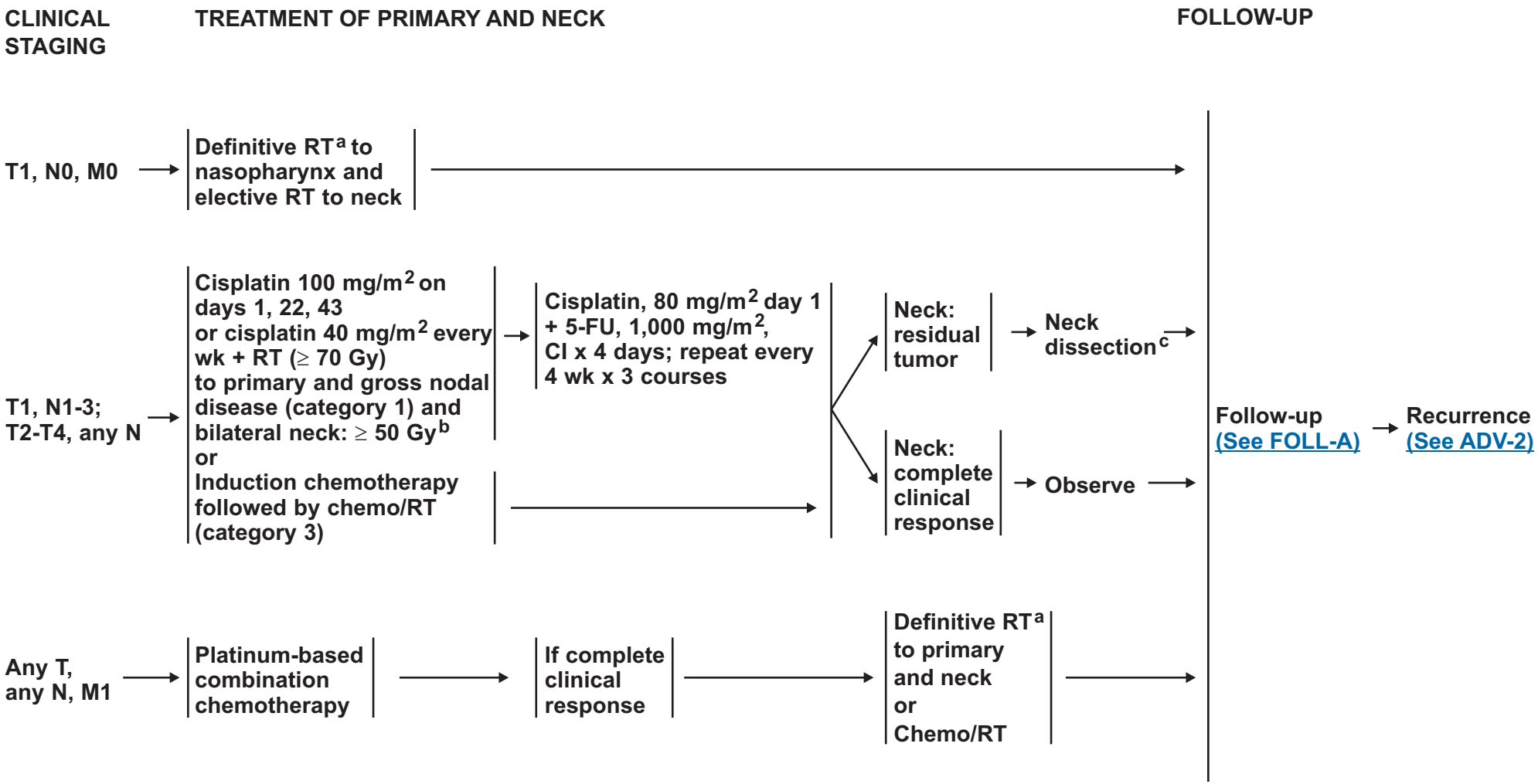
CLINICAL STAGING



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

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

- **Primary and gross adenopathy: 66-70 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)**

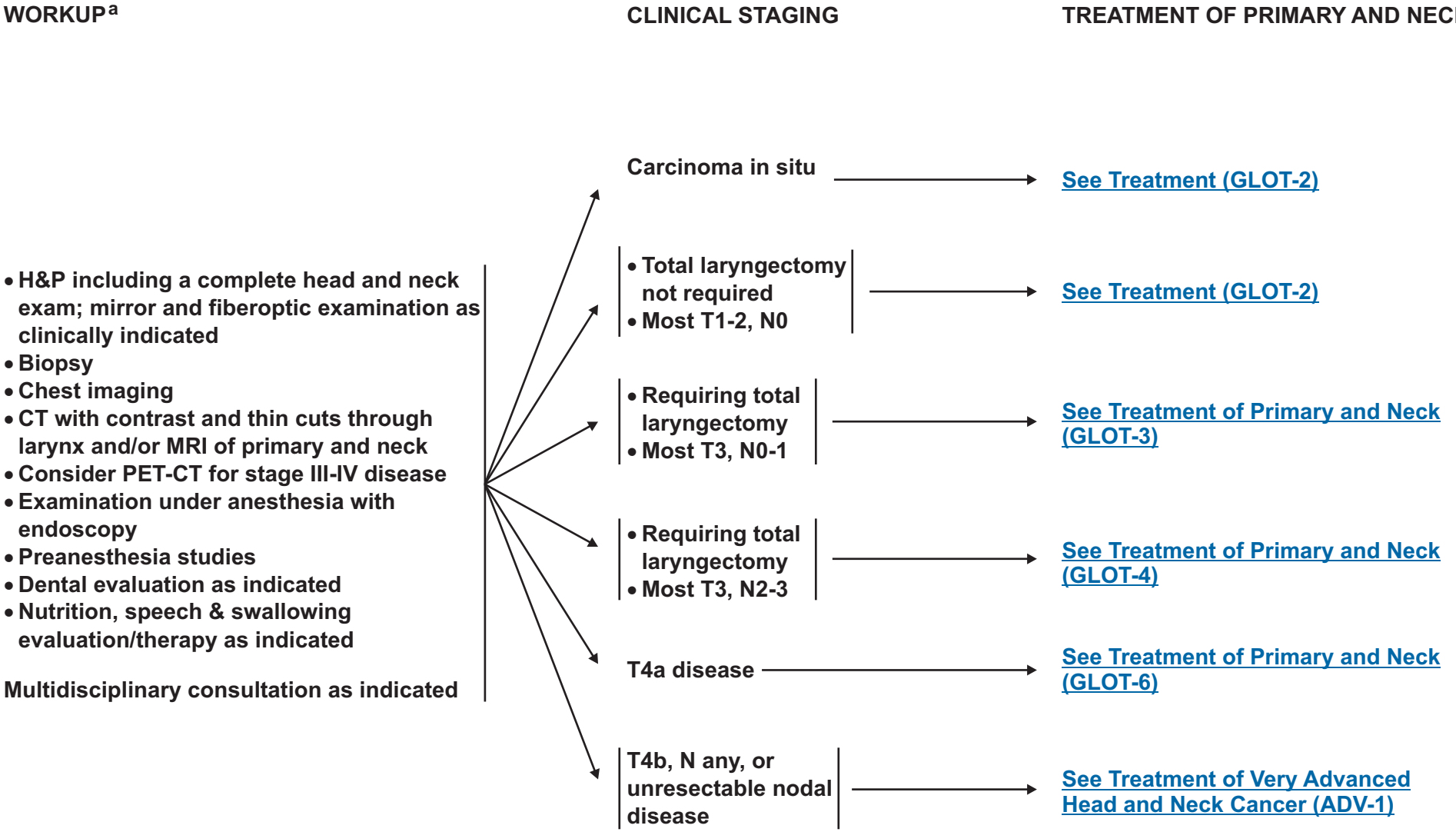
IMRT is a preferred technique in cancer of the nasopharynx to minimize dose to critical structures.

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

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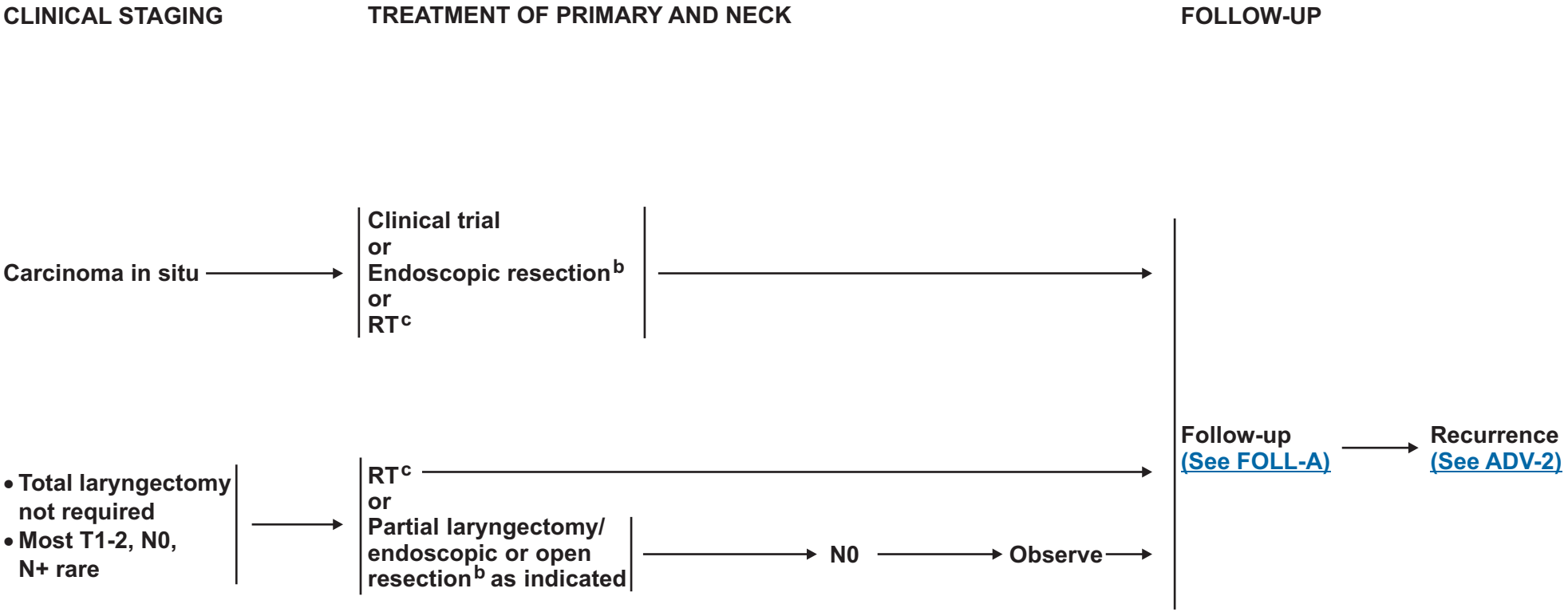


[a]Complete workup not indicated for Tis, T1.

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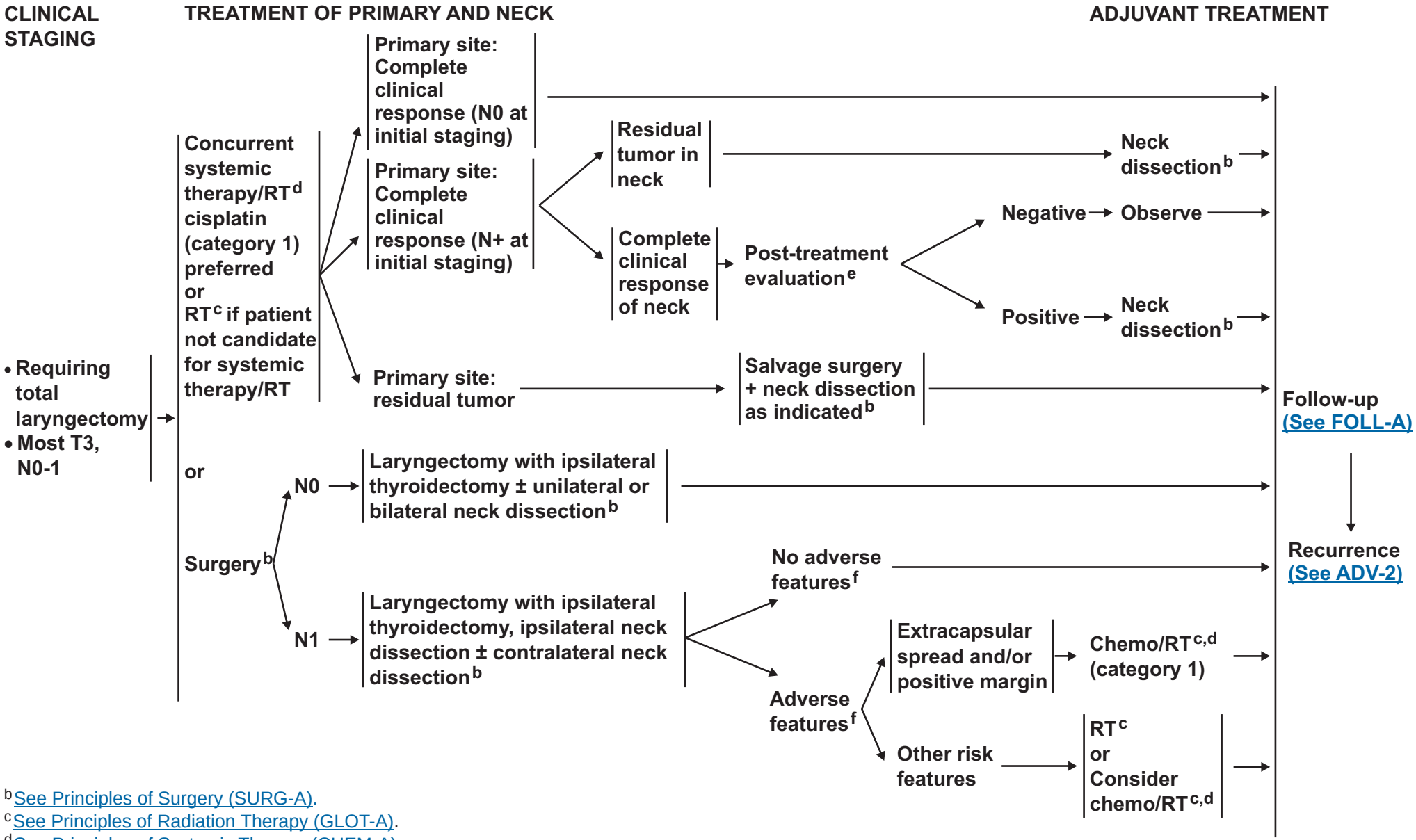


[b] See Principles of Surgery (SURG-A).
[c] See Principles of Radiation Therapy (GLOT-A).

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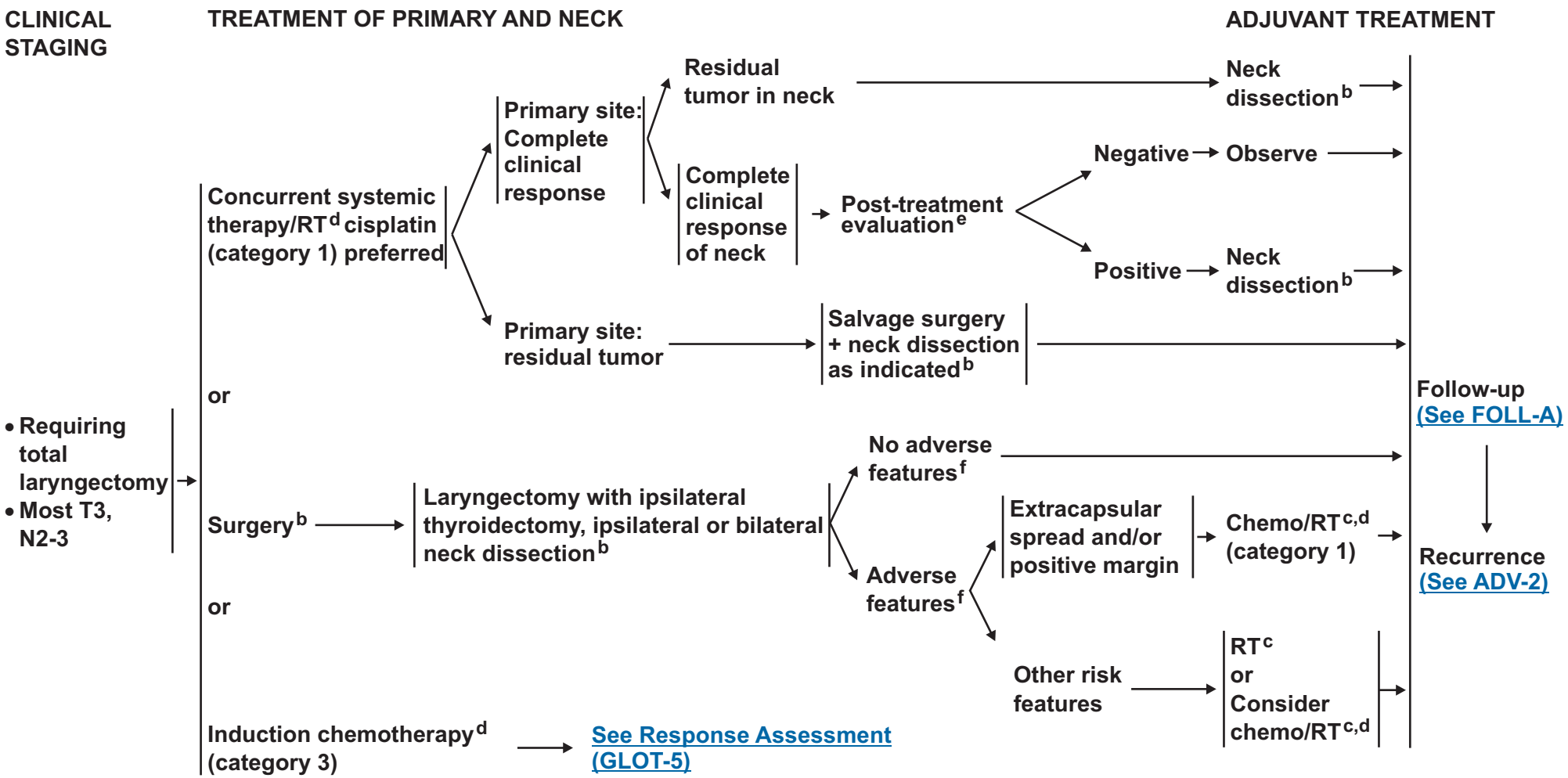


[b] See Principles of Surgery (SURG-A).
[c] See Principles of Radiation Therapy (GLOT-A).
[d] See Principles of Systemic Therapy (CHEM-A).
[e] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).
[f] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal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

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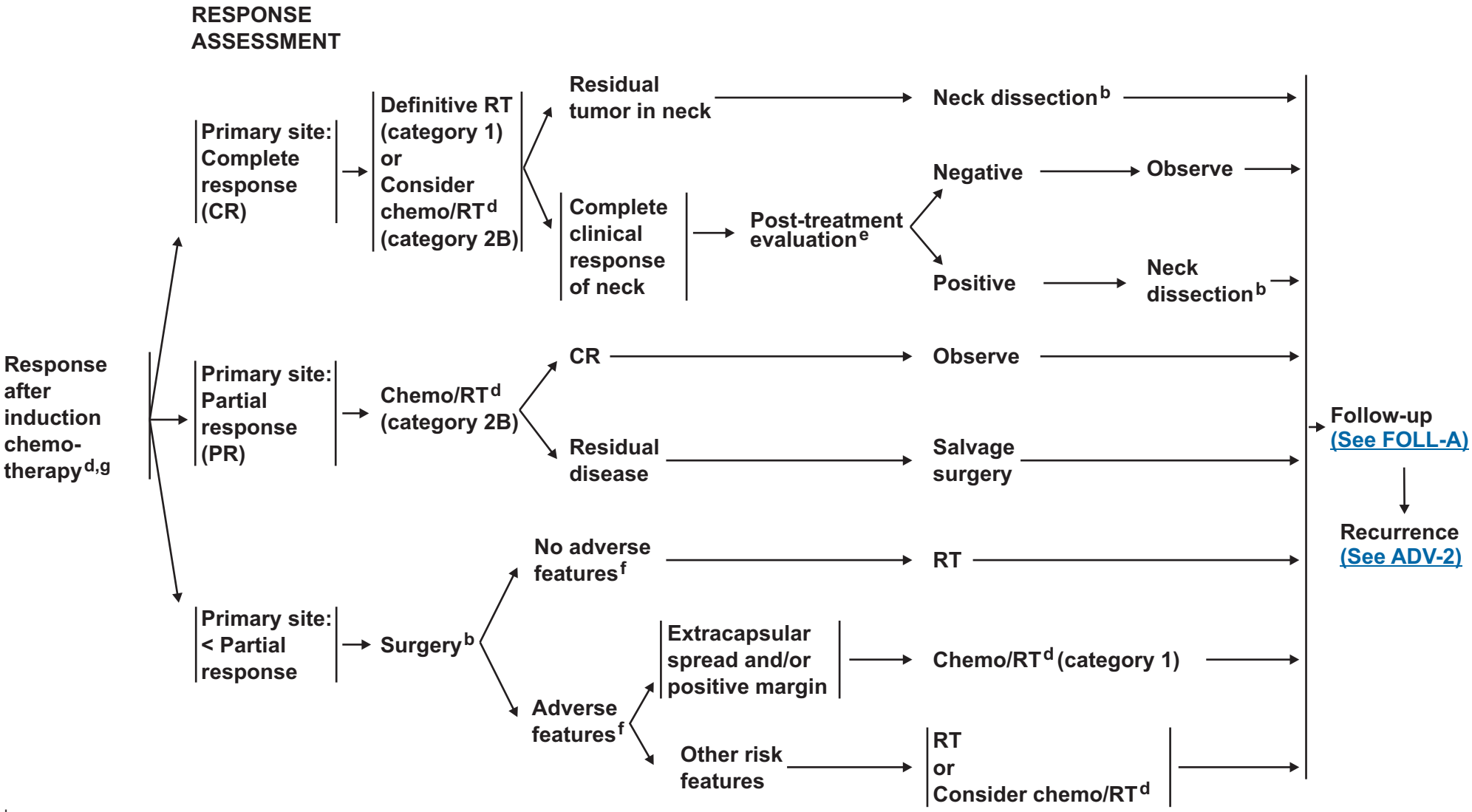


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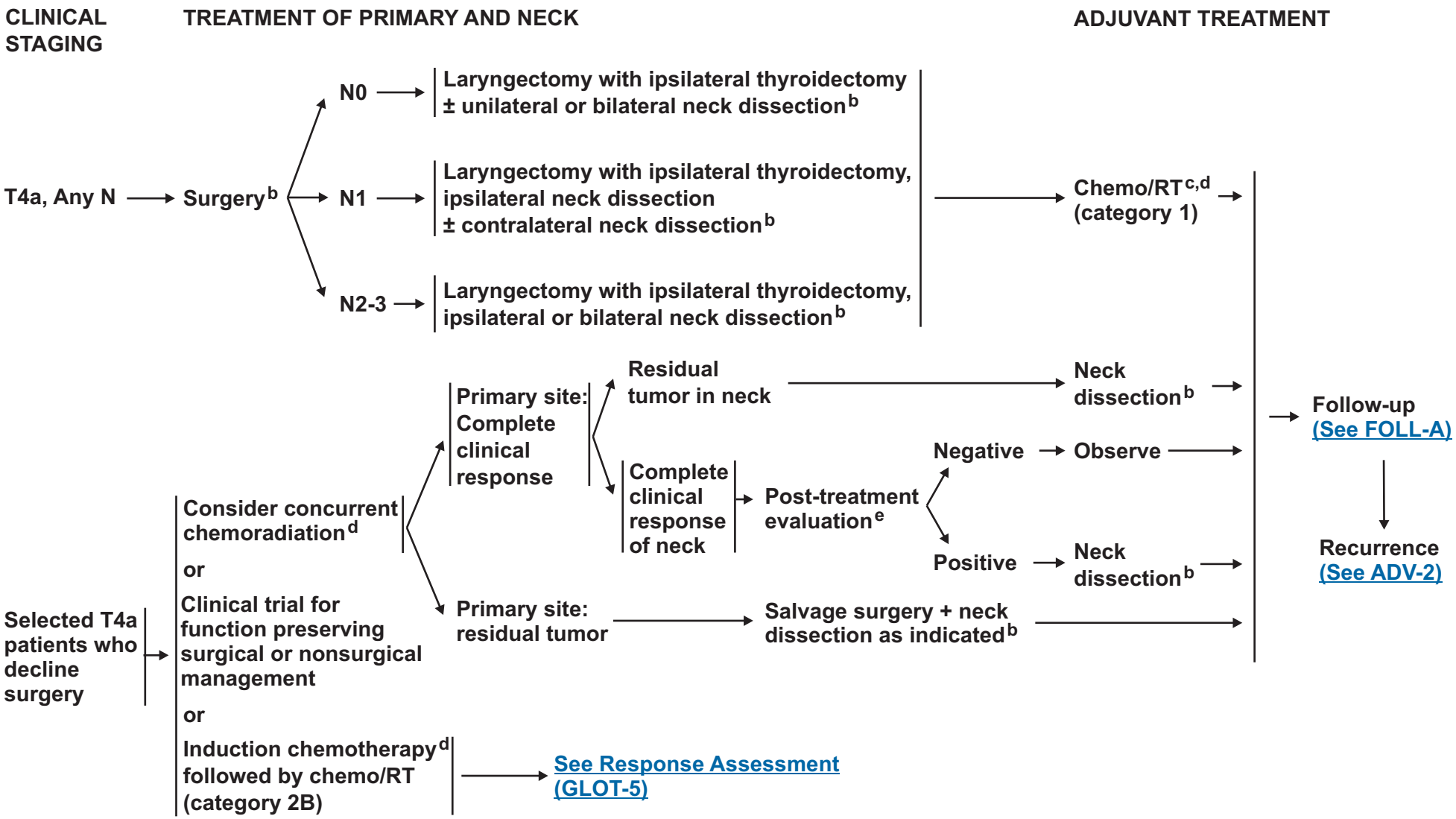


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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

- T1, N0: 63-66 Gy in 2.25-2.0 Gy/fraction
- T1-2: > 66 Gy using conventional fractionation (2.0 Gy/fraction)
- ≥ T2 and gross adenopathy:
  Conventional fractionation: 70 Gy (2.0 Gy/fraction) in 7 weeks
  Altered fractionation:
  - Concomitant boost accelerated RT: 72 Gy/6 weeks
    (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation: 79.2-81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
- Uninvolved nodal stations:
  44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative RT

- Indicated for pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
- Preferred interval between resection and postoperative RT is ≤ 6 weeks.
- Primary: 60-66 Gy (2.0 Gy/fraction)
- Neck
  - Involved nodal stations:
    60-66 Gy (2.0 Gy/fraction)
  - Uninvolved nodal stations:
    44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative chemoradiation

- Indicated for extracapsular nodal spread and/or positive margins[2-4]
- Consider for other risk features: pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism
- Concurrent single agent cisplatin at 100 mg/m^2 every 3 wks is recommended.

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

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

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WORKUP

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

Multidisciplinary consultation as indicated

CLINICAL STAGING

- Not requiring total laryngectomy
- Most T1-2, N0

→ See Treatment of Primary and Neck (SUPRA-2)

- Requiring total laryngectomy
- T3, N0

→ See Treatment of Primary and Neck (SUPRA-3)

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

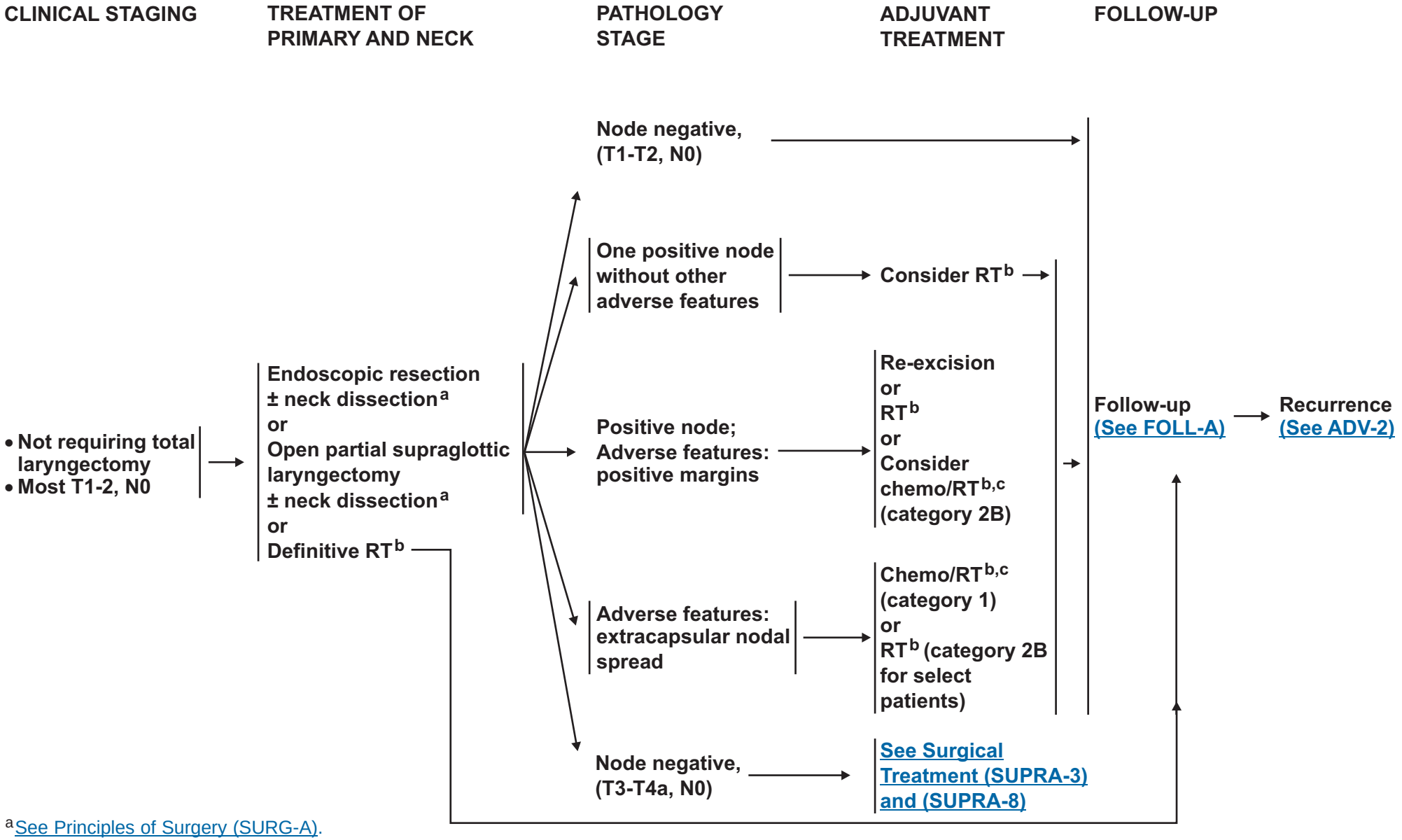
Node positive disease → See Clinical Staging (SUPRA-4)

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

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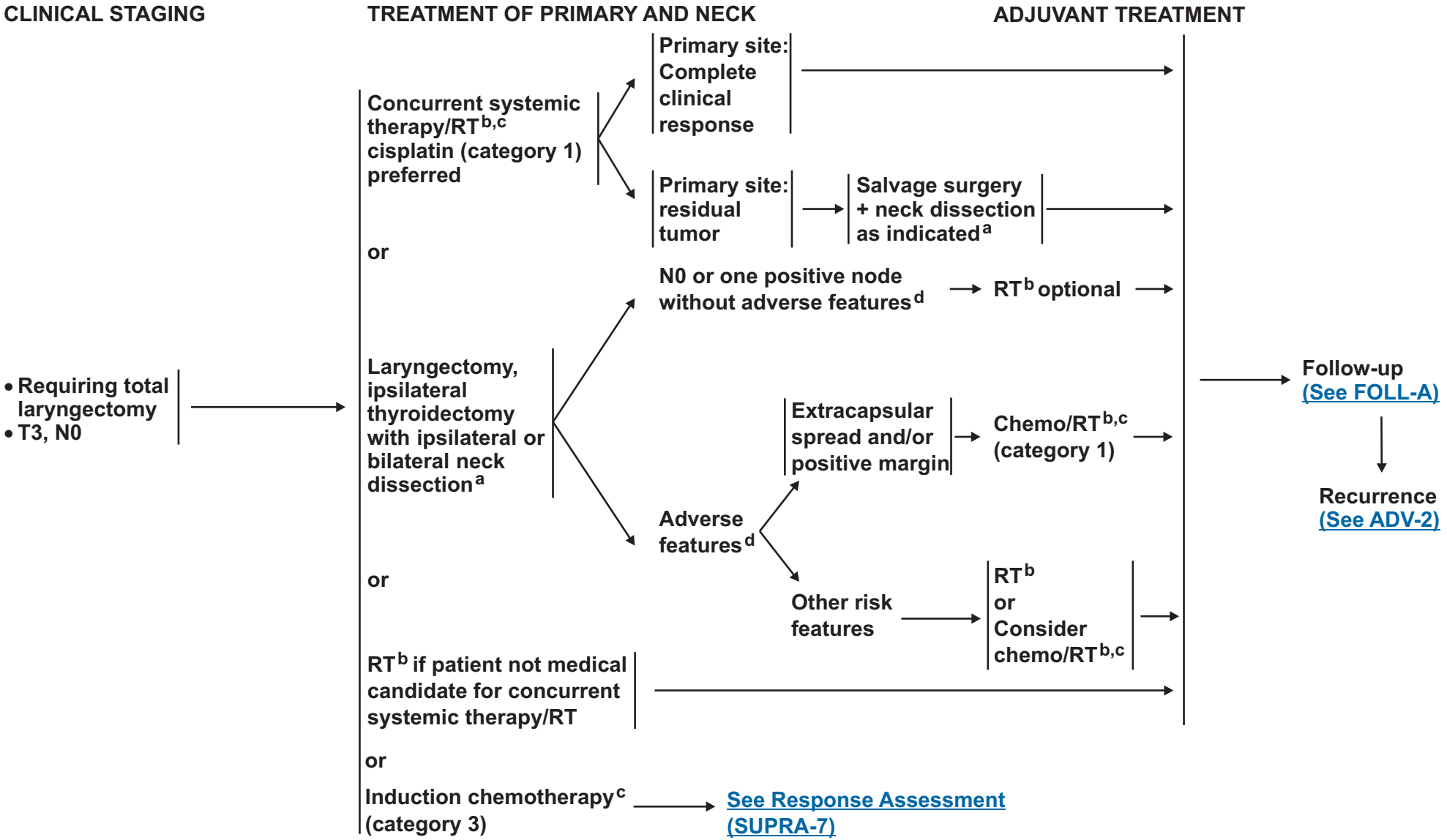


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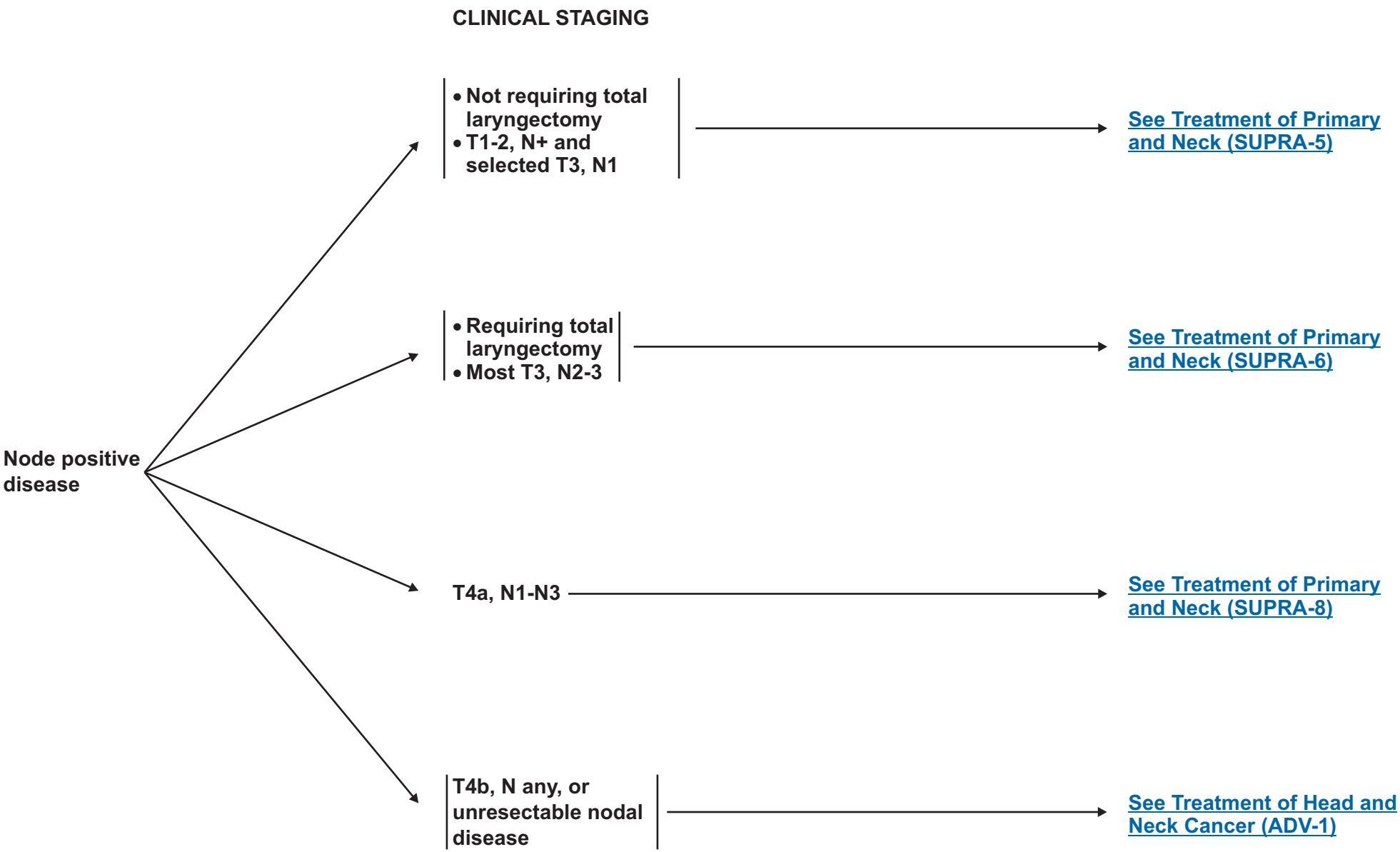


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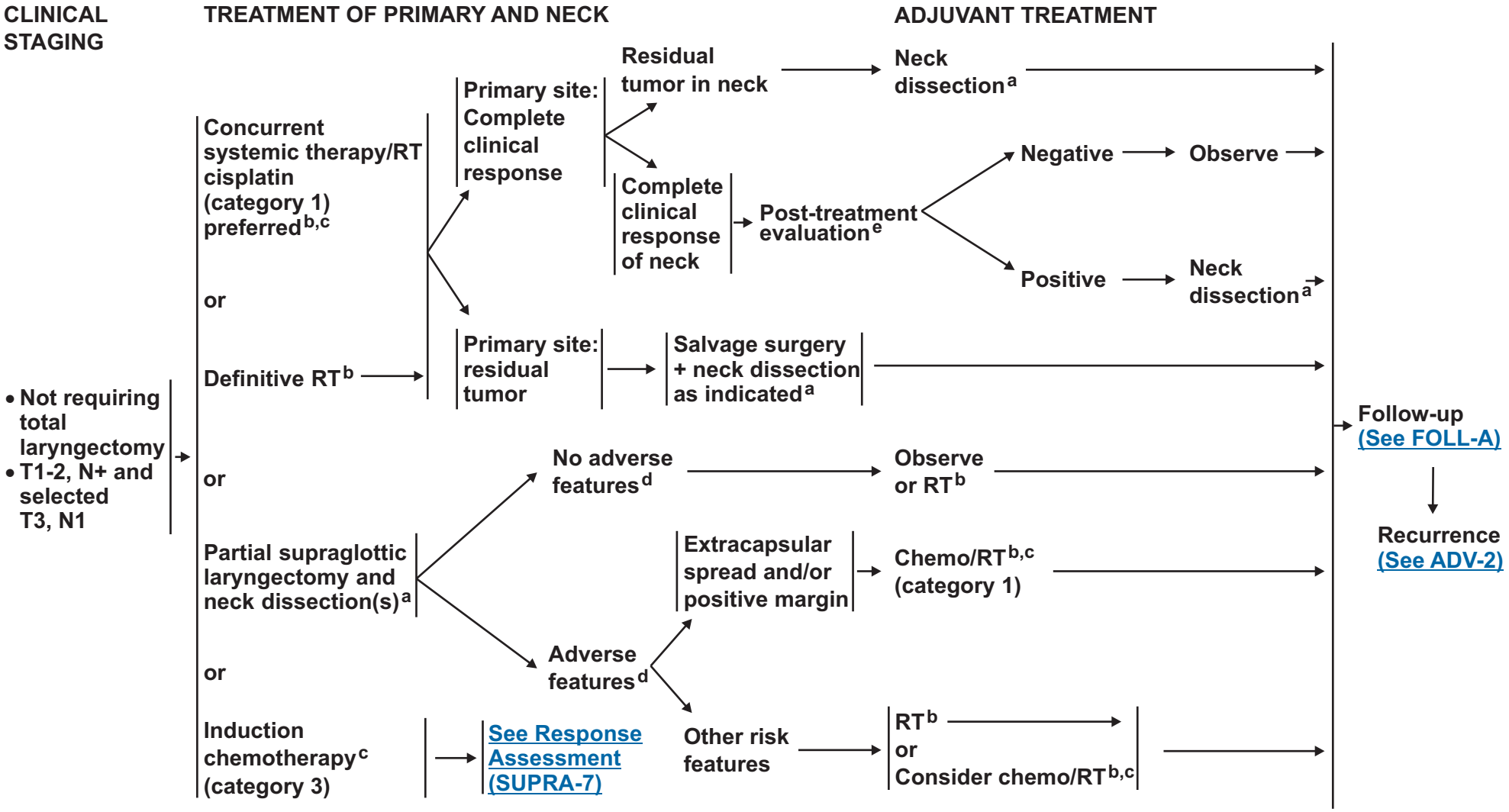
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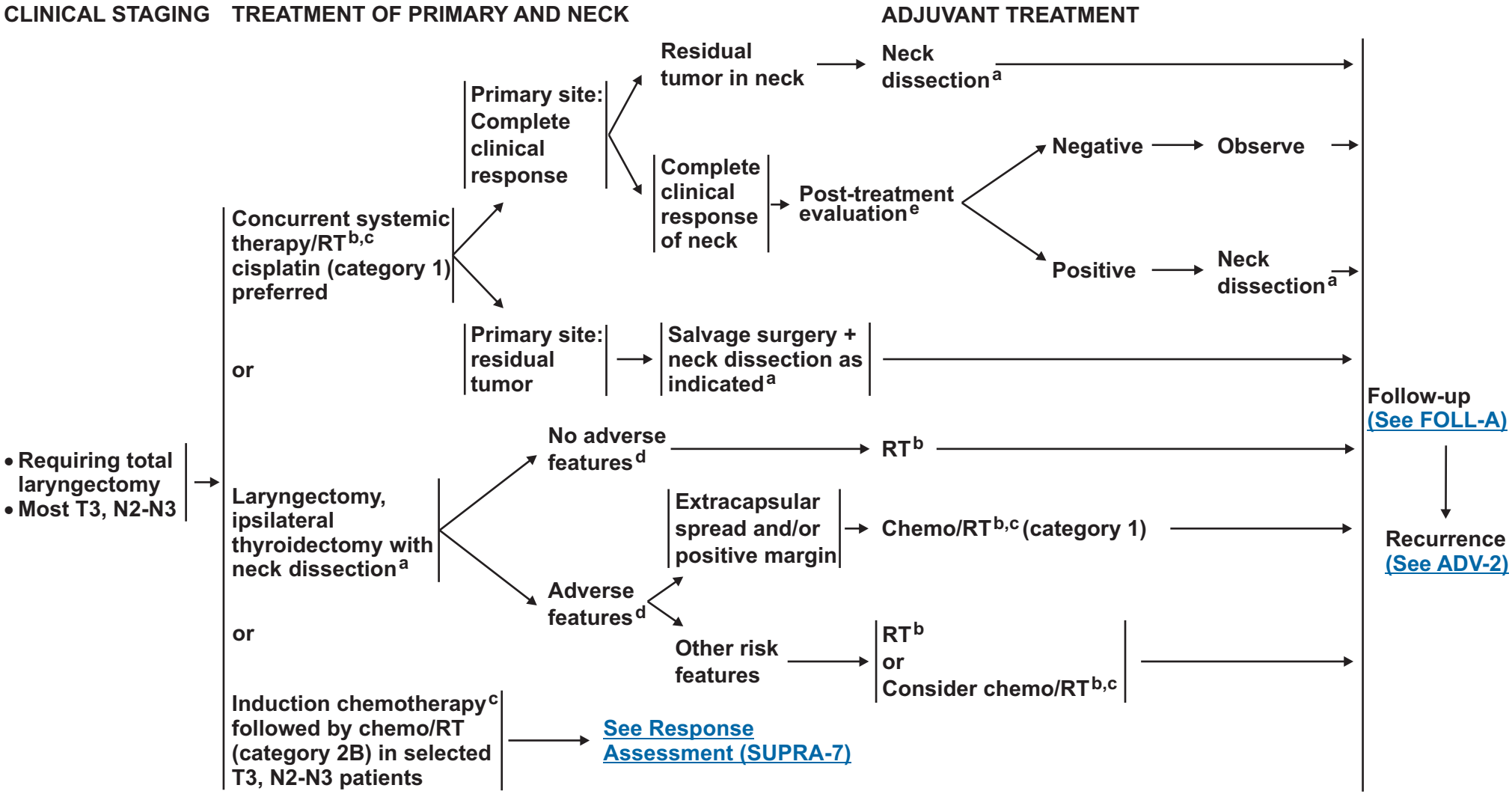


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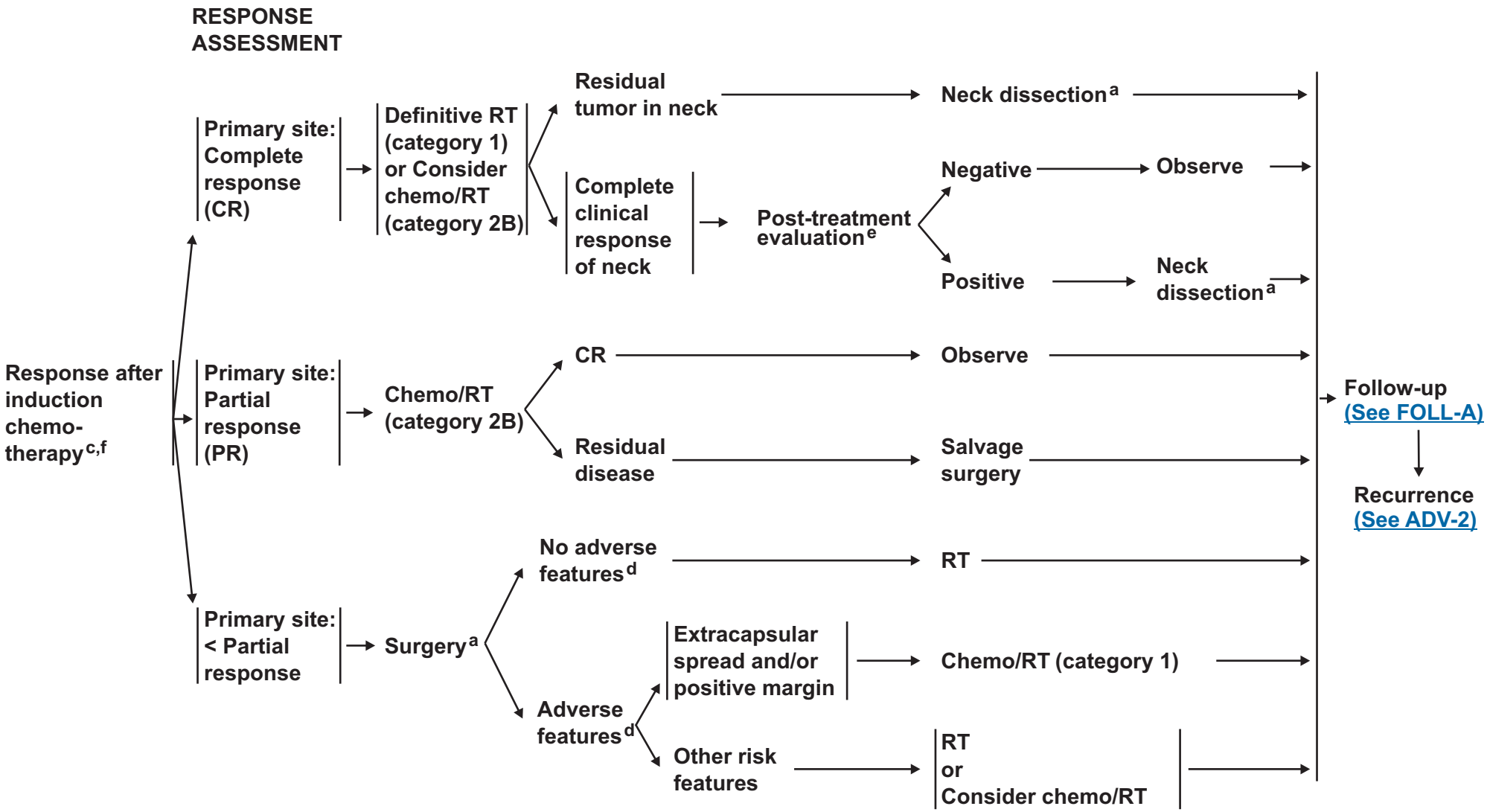


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[c] See Principles of Systemic Therapy (CHEM-A).
[d] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
[e] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).

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

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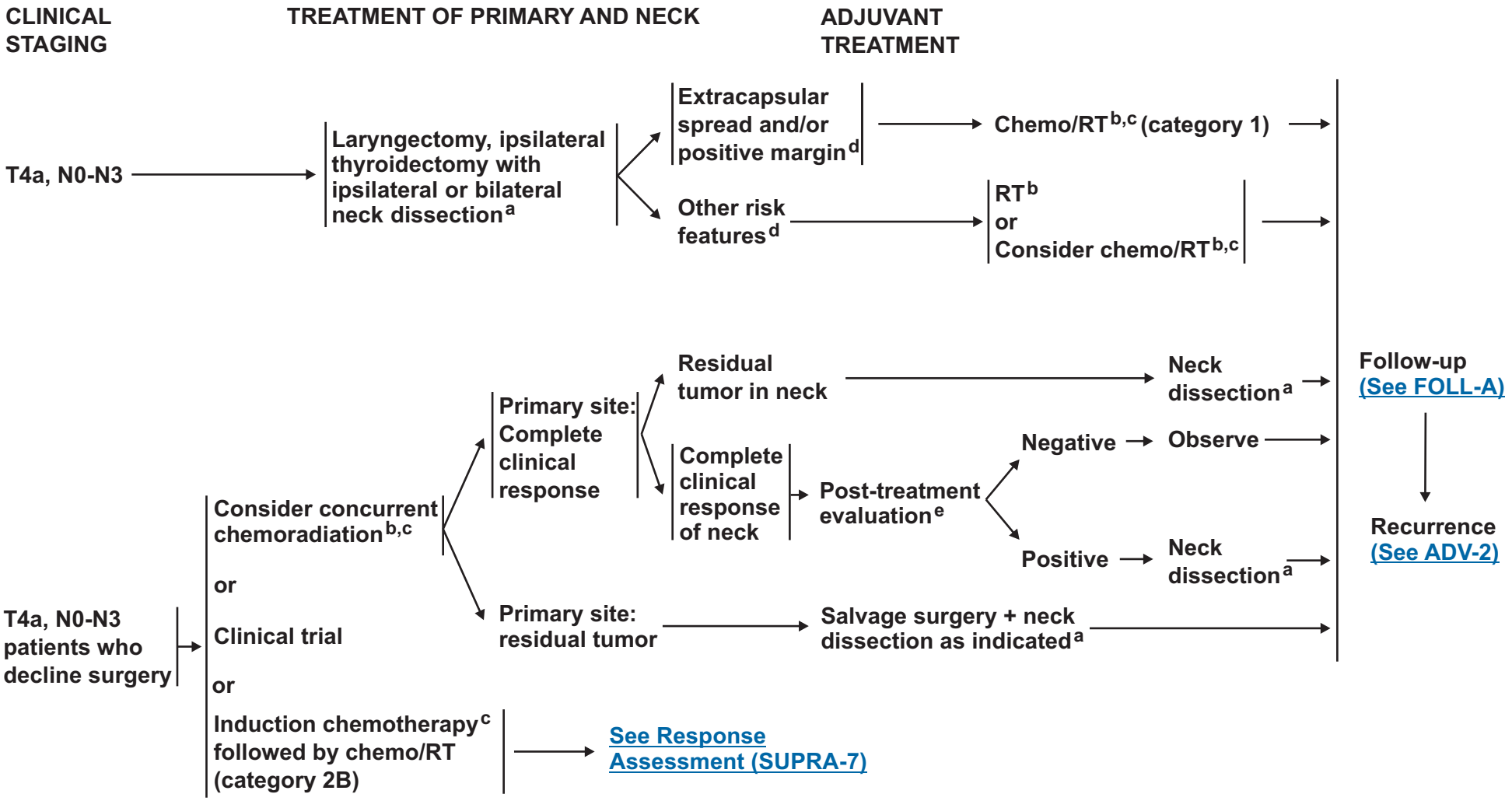


[a] See Principles of Surgery (SURG-A).
[c] See Principles of Systemic Therapy (CHEM-A).
[d] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
[e] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).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

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

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

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

T2-3, N0-1:

- **Conventional fractionation:**
  Primary and gross adenopathy: ≥ 70 Gy (2.0 Gy/fraction)
  Neck, uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)
- **Altered fractionation:**
  - **6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.**
  - **Concomitant boost accelerated RT:**
    72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - **Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction twice daily)**
- **Neck**
  - **Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)**

Chemoradiation

Concurrent platinum plus 70 Gy/7 weeks conventional

Postoperative RT

- **Indicated for pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.**
- **Preferred interval between resection and postoperative RT is ≤ 6 weeks.**
- **Primary: 60-66 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Involved nodal stations: 60-66 Gy (2.0 Gy/fraction)**
  - **Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)**

Postoperative chemoradiation

- **Indicated for extracapsular nodal spread and/or positive margins[2-4]**
- **Consider for other risk features: pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.**
- **Concurrent single agent cisplatin at 100 mg/m^2 every 3 wks is recommended.**

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

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

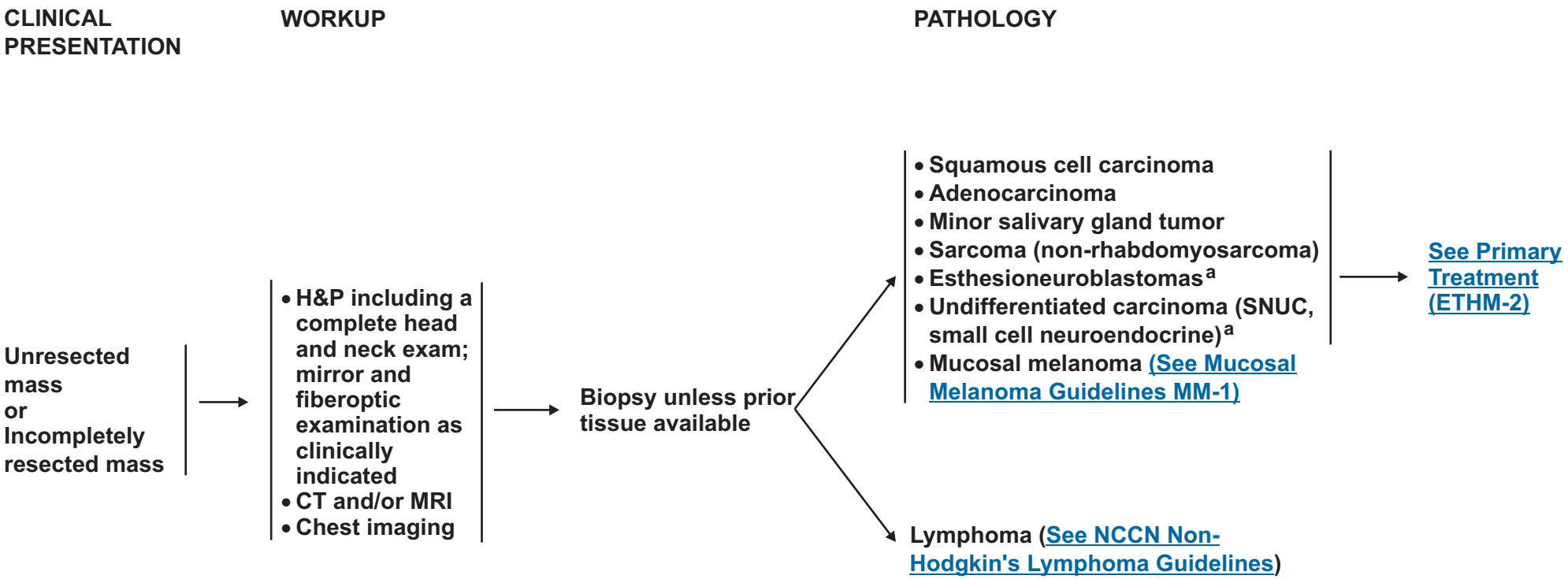
[3] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.

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

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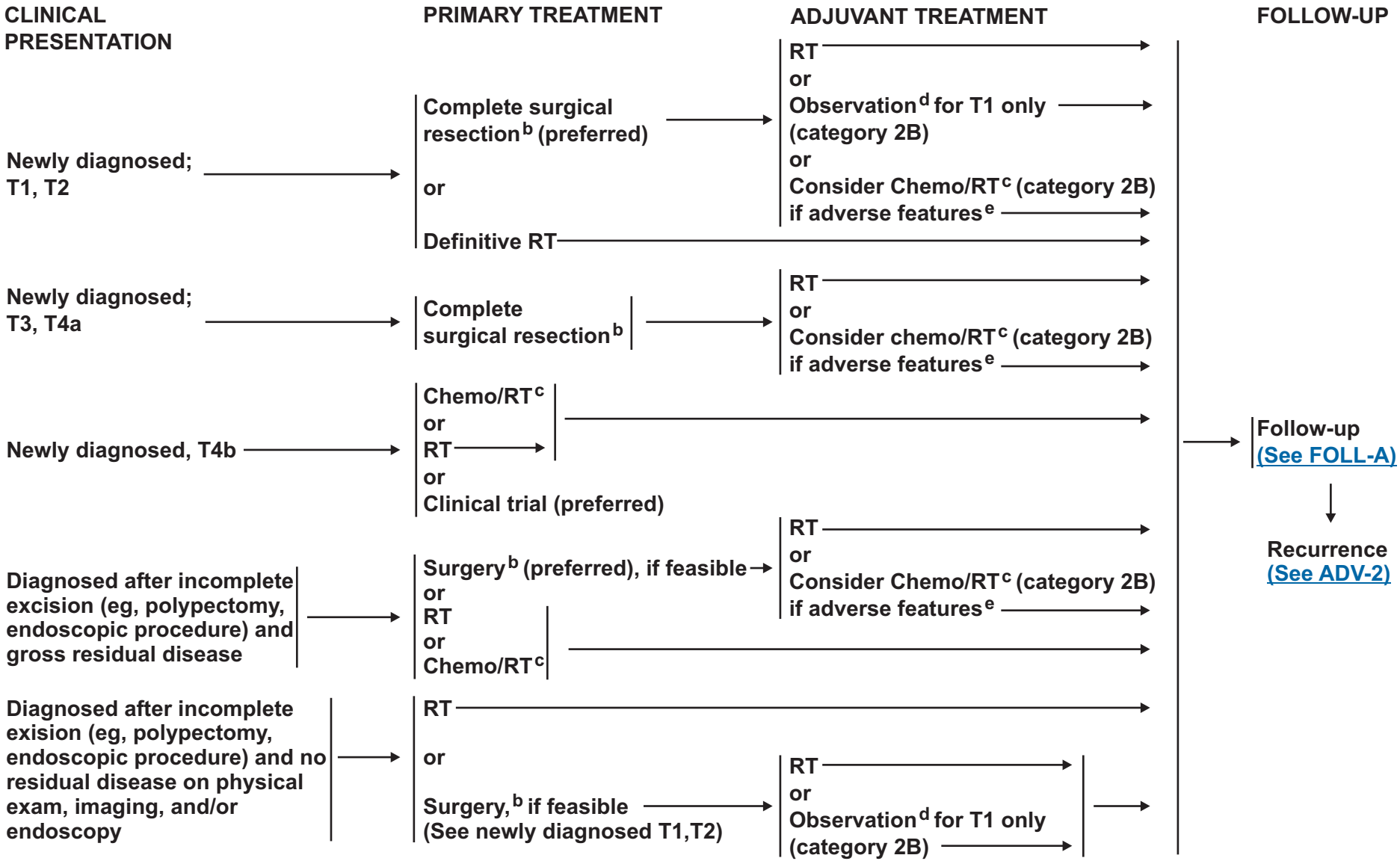
[a]For sinonasal undifferentiated carcinoma (SNUC), esthesioneuroblastoma, and small cell neuroendocrine histologies, systemic therapy should be a part of the overall treatment.

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Head and Neck Cancers
Ethmoid Sinus Tumors

Guidelines Index
Head and Neck Cancers TOC
Staging, Discussion, References



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

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

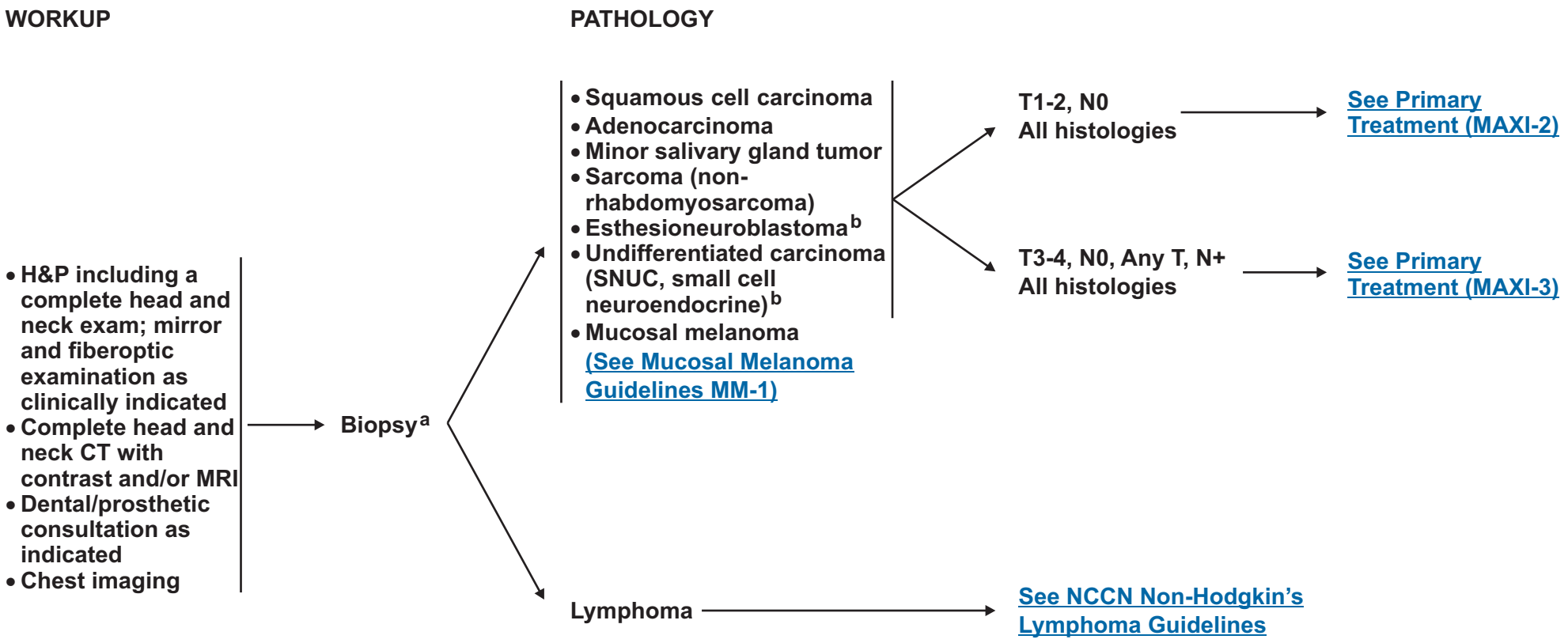
[d] Pathologic features: Negative margins, favorable histology, central tumors, low grade tumors.

[e] Adverse features include positive margins and intracranial extension.

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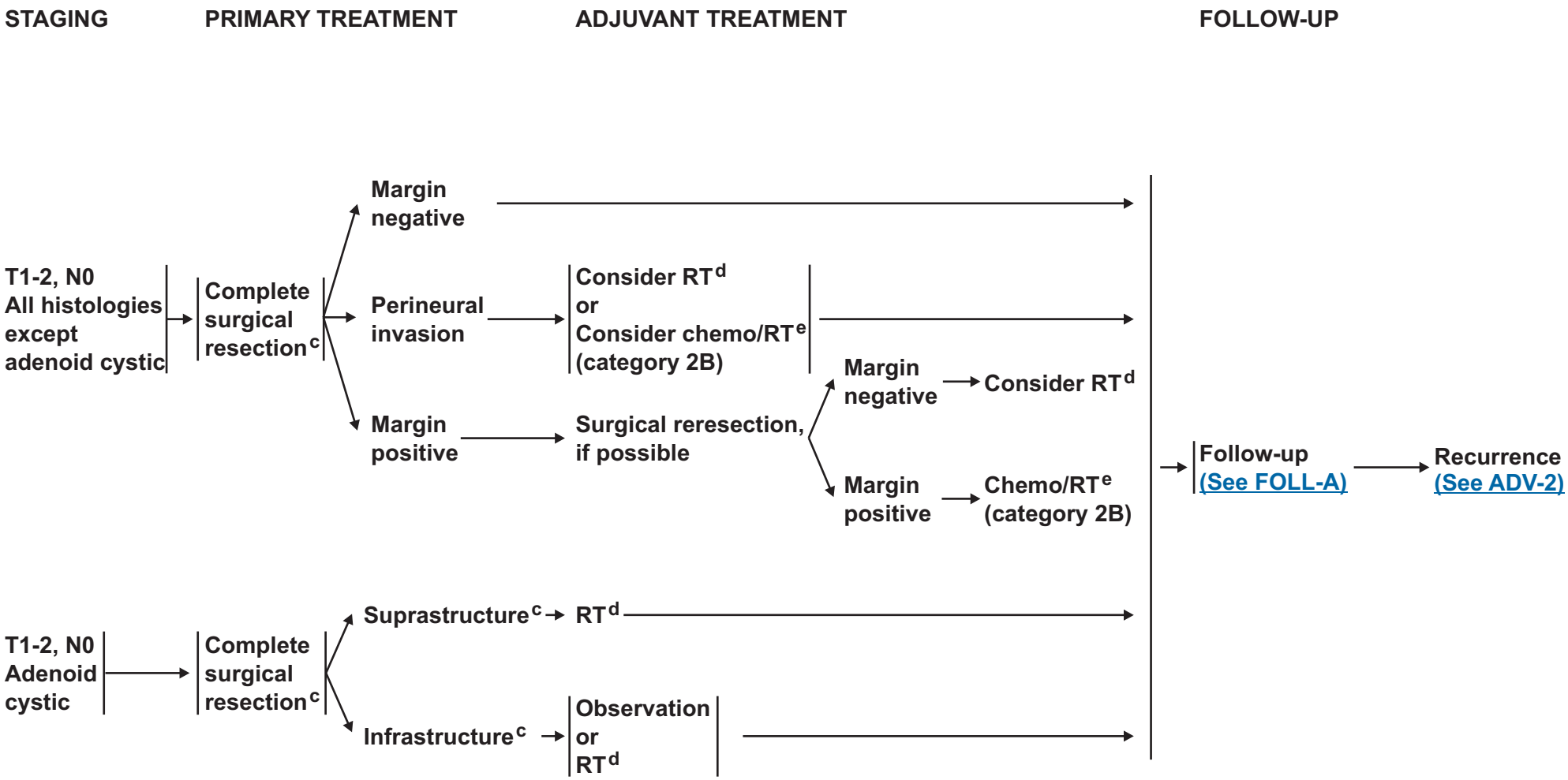
[a]Biopsy:
- Preferred route is transnasal.
- Needle biopsy may be acceptable.
- Avoid canine fossa puncture or Caldwell-Luc approach.

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

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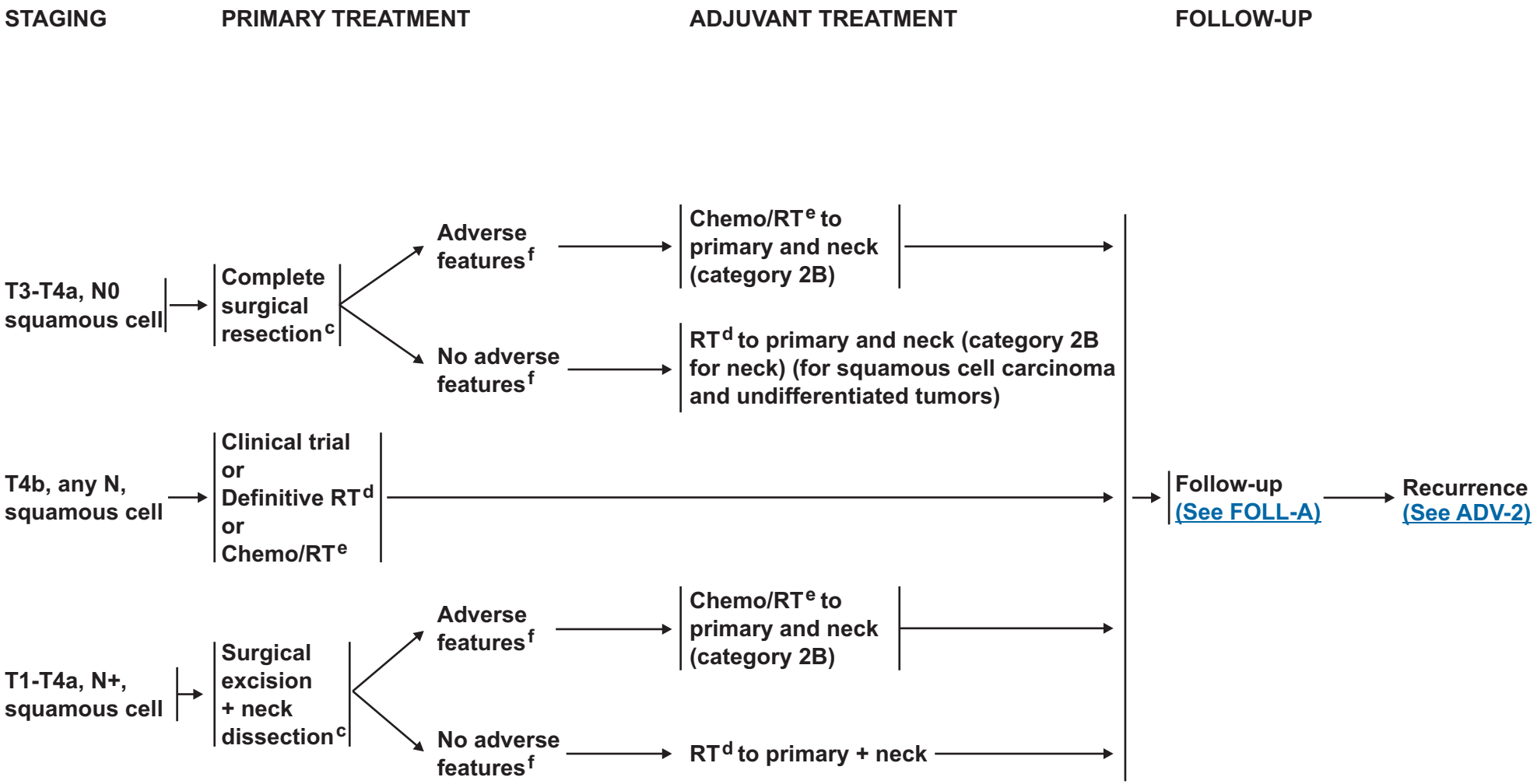


[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MAXI-A).
[e] See Principles of Systemic Therapy (CHEM-A).

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

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

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

Postoperative RT

- **Primary: 60-66 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Involved nodal stations: 60-66 Gy (2.0 Gy/fraction)**
  - **Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)**

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

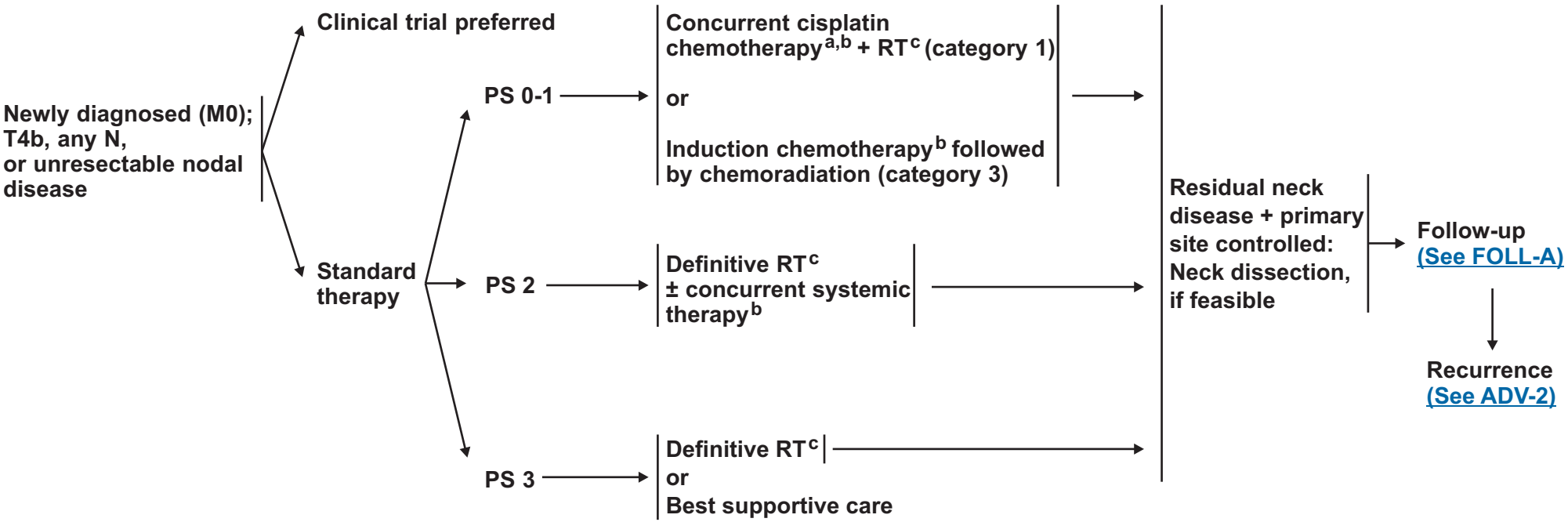
[1] See Radiation Techniques (RAD-A).

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DIAGNOSIS **TREATMENT OF HEAD AND NECK CANCER**



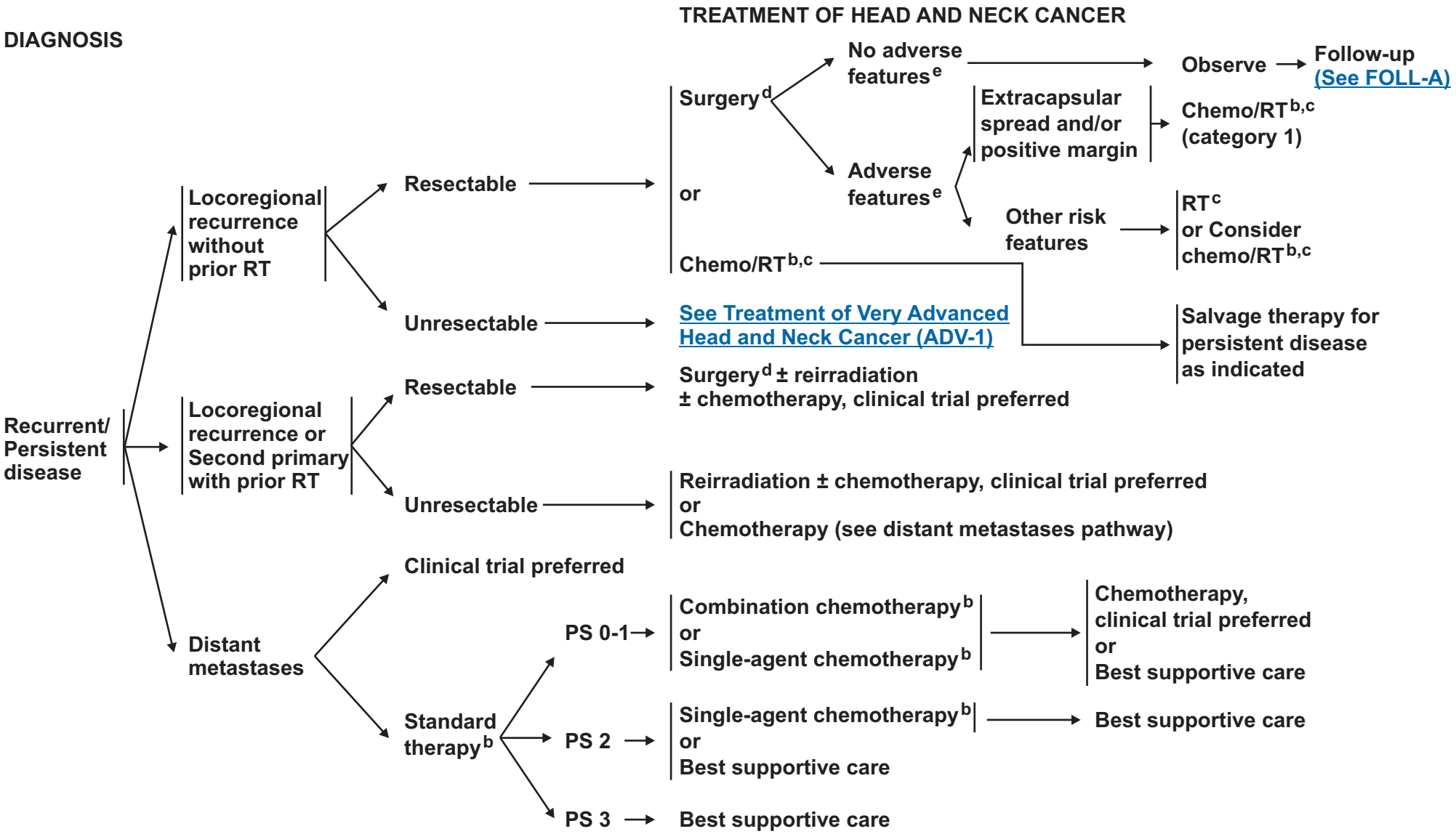
[a]The single-agent cisplatin or carboplatin chemoradiotherapy regimens have not been compared in randomized trials. Therefore, no optimal standard regimen is defined. Combination chemotherapy regimens are more toxic and have not been directly compared to single-agent regimens.

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

[c]See Principles of Radiation Therapy (ADV-A).

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[b] See Principles of Systemic Therapy (CHEM-A).
[c] See Principles of Radiation Therapy (ADV-A).
[d] See Principles of Surgery (SURG-A).
[e] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

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

Concurrent chemoradiation (preferred)

Conventional fractionation:

- **Primary and gross adenopathy: ≥ 70 Gy (2.0 Gy/fraction)**
- **Neck**
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)

Chemoradiation

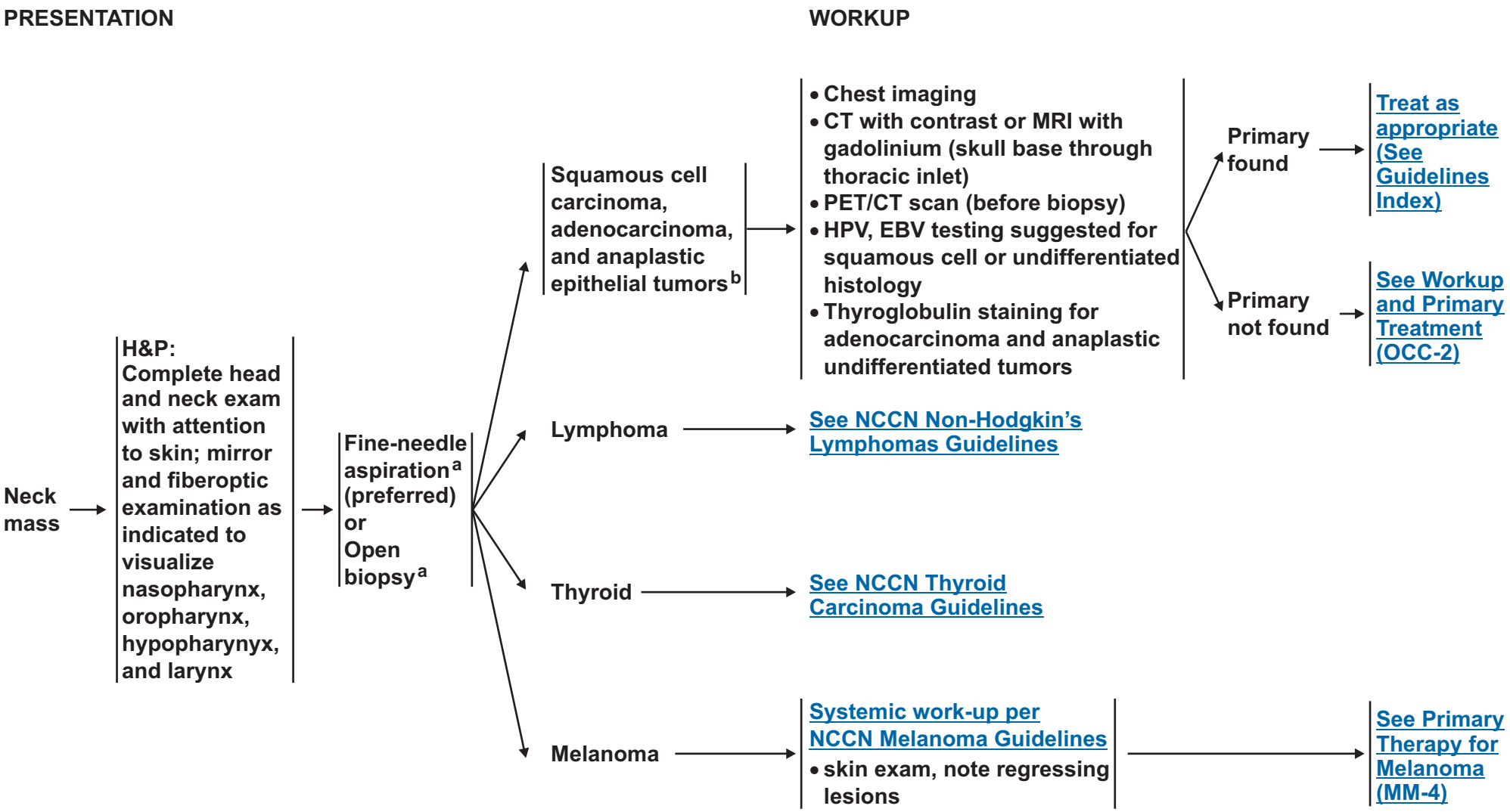
Based on published data, concurrent chemoradiation typically uses conventional fractionation at 2.0 Gy/fraction to ≥ 70 Gy in 7 wks with single agent cisplatin given every 3 wks at 100 mg/m^2 x 3 doses. Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy or altered fractionation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

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

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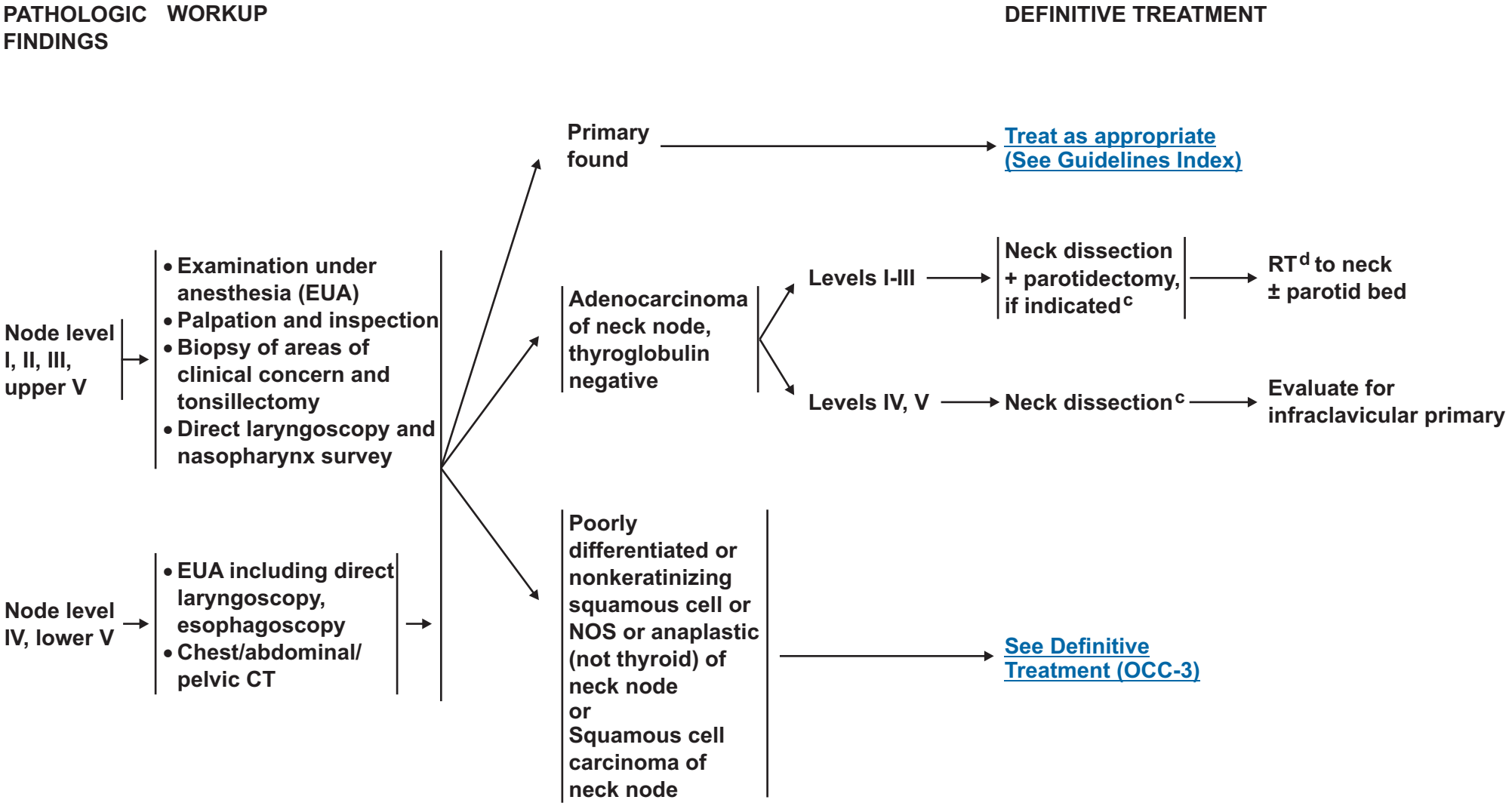
[a] Repeat FNA, core, or open biopsy may be necessary for uncertain or non-diagnostic histologies. Patient should be prepared for neck dissection at time of open biopsy, if indicated.

[b] Determined with appropriate immunohistochemical stains.

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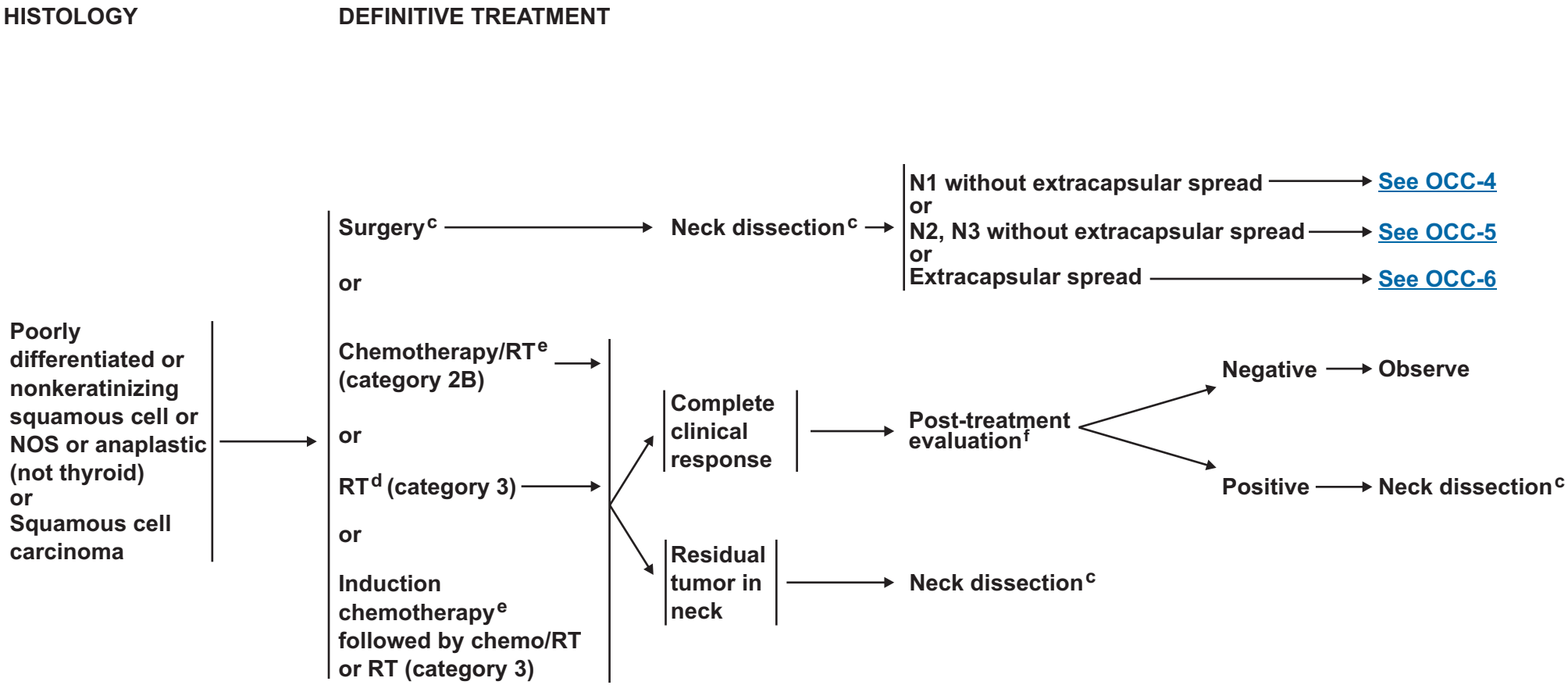


[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (OCC-A).

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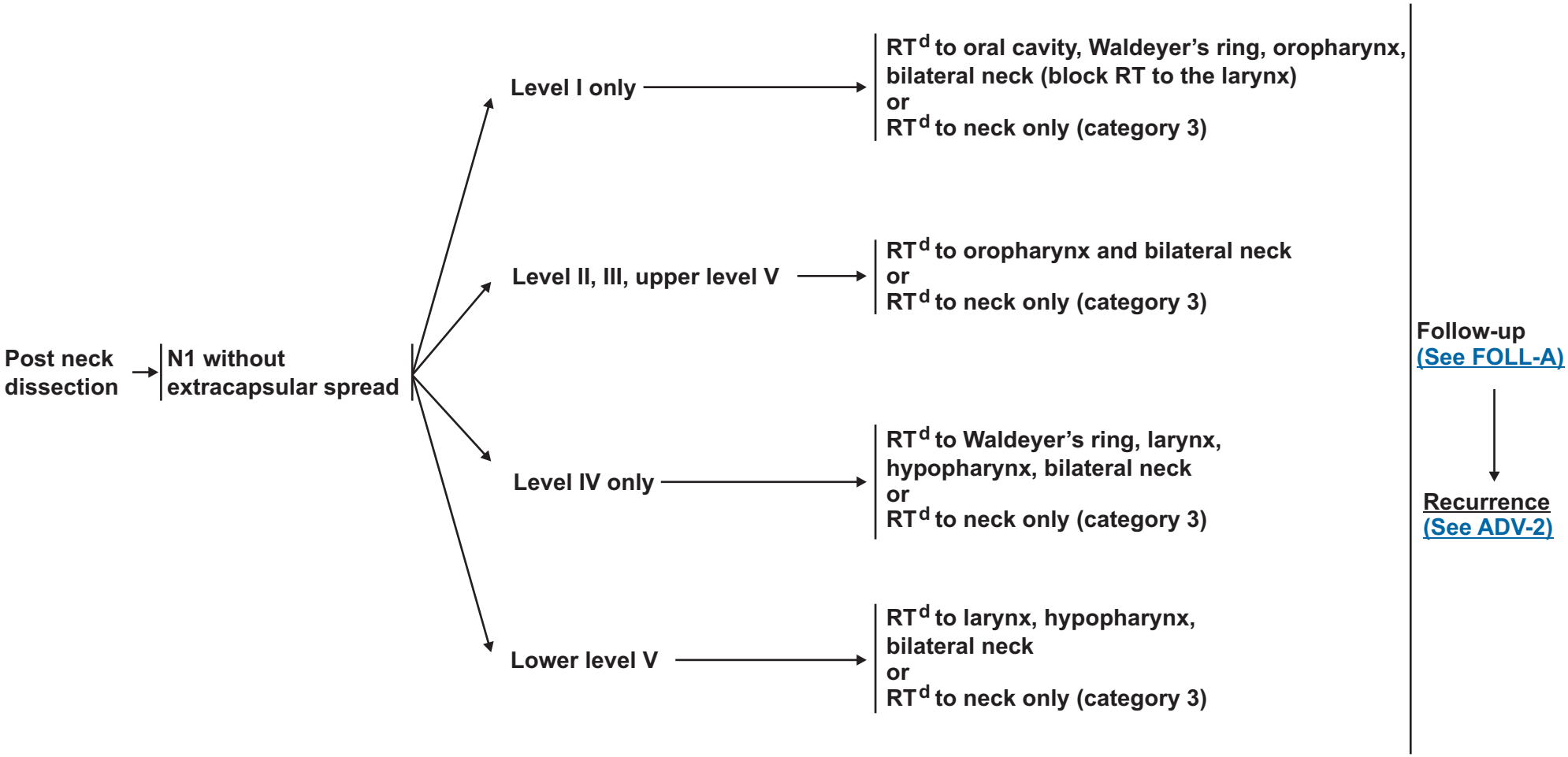


[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (OCC-A).
[e] See Principles of Systemic Therapy (CHEM-A).
[f] See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).

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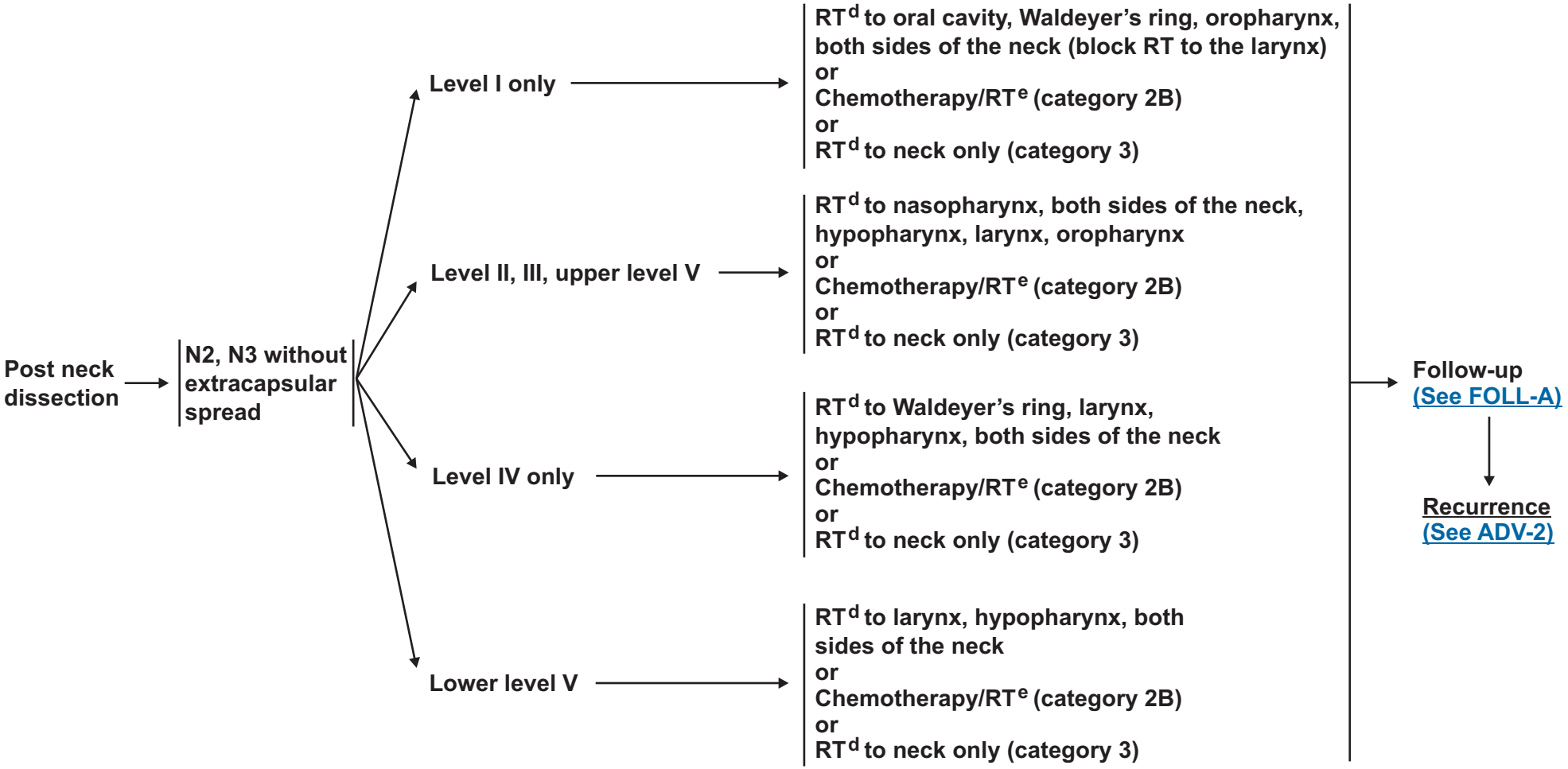


[d] See Principles of Radiation Therapy (OCC-A).

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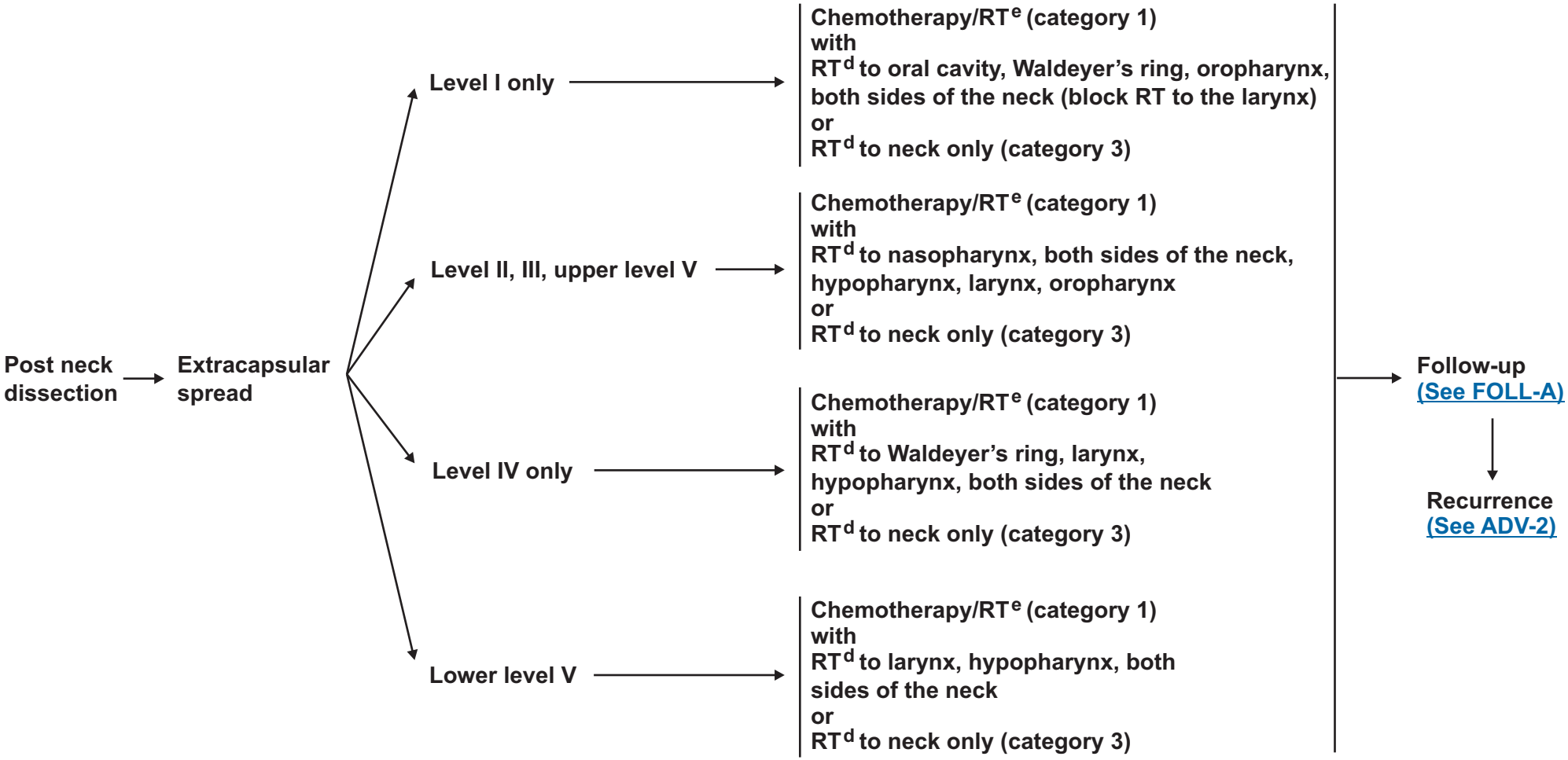


[d] See Principles of Radiation Therapy (OCC-A).
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PRINCIPLES OF RADIATION THERAPY[1,2]

Gross Adenopathy:

Altered fractionation:

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

Mucosal dosing:

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

Neck

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

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

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CLINICAL PRESENTATION

WORKUP

Unresected salivary gland mass
- **Parotid**
- **Submandibular**
- **Minor salivary gland**[a]

or

Incompletely resected salivary gland mass

→

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

→ **Clinically benign**[c] **or Carcinoma** → **See SALI-2**

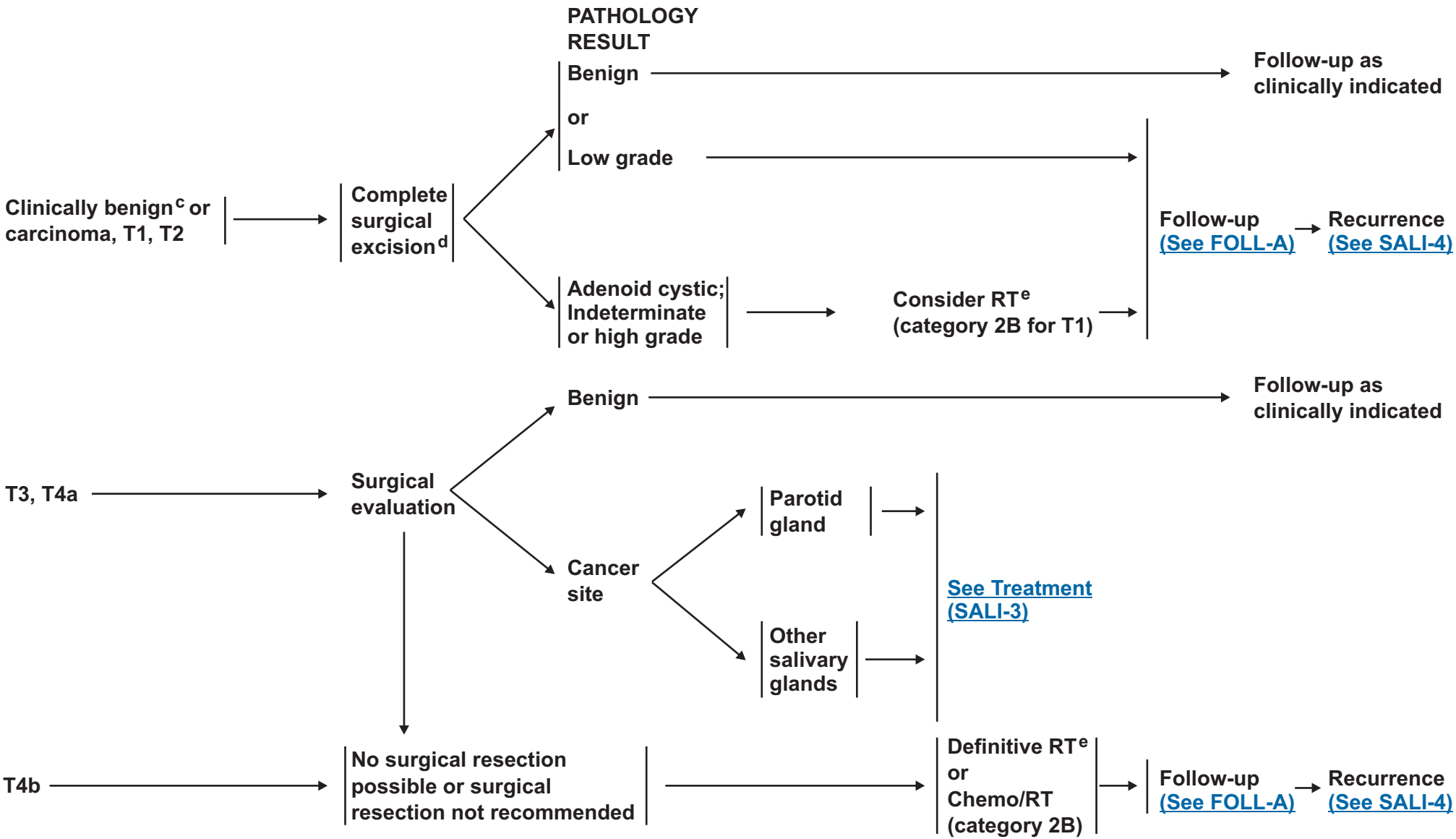
→ **Lymphoma** → **See NCCN Non-Hodgkin's Lymphomas Guidelines**

[a] Site and stage determine therapeutic approaches.
[b] For advanced cancer, includes CT/MRI: base of skull to clavicle.
[c] Characteristics of benign tumor include mobile superficial lobe, slow growth, painless, VII intact, and no neck nodes.

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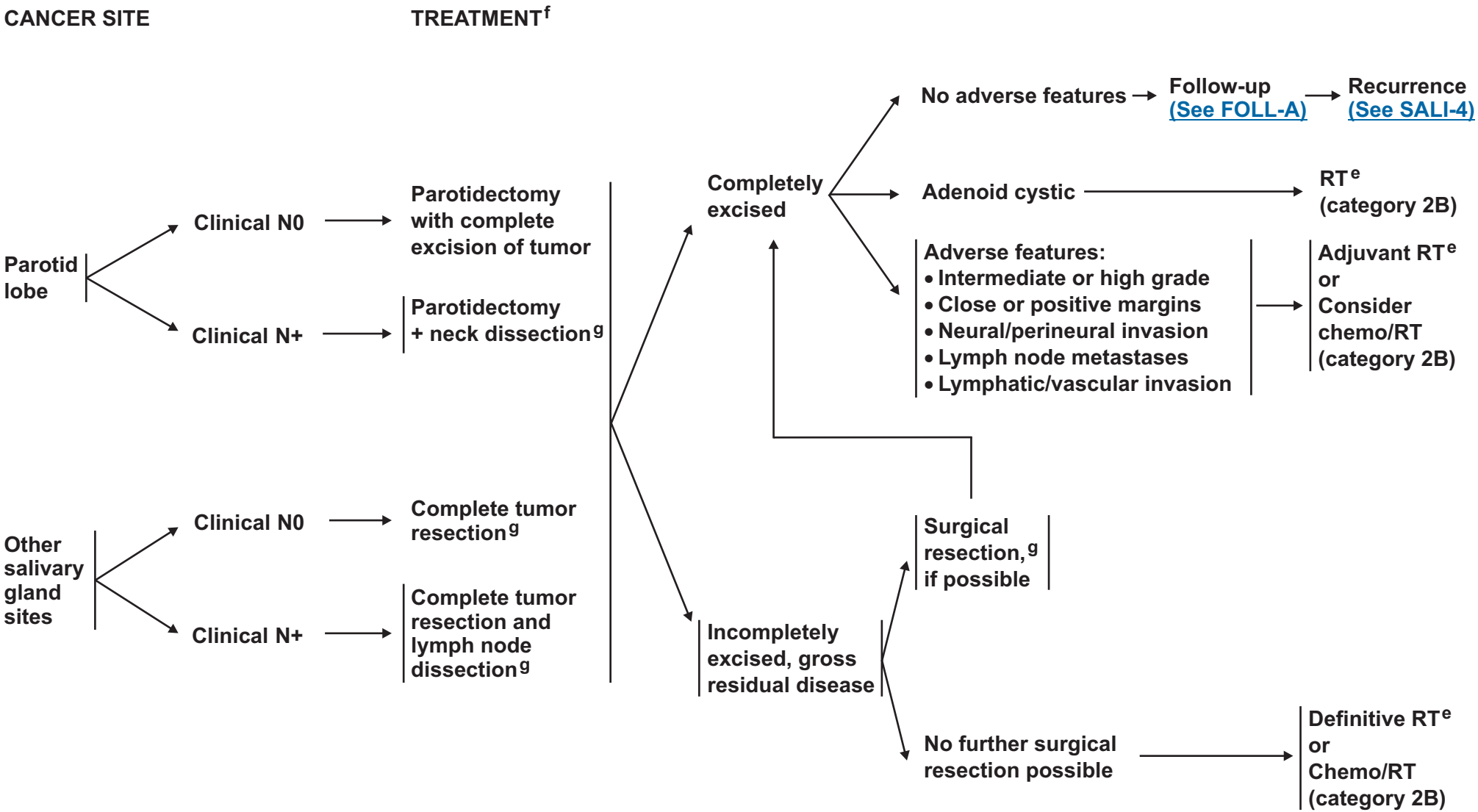


[c] Characteristics of benign tumor include mobile superficial lobe, slow growth, painless, VII intact, and no neck nodes.
[d] Surgical excision of clinically benign tumor: no enucleation of lateral lobe, intraoperative communication with pathologist if indicated.
[e] See Principles of Radiation Therapy (SALI-A).

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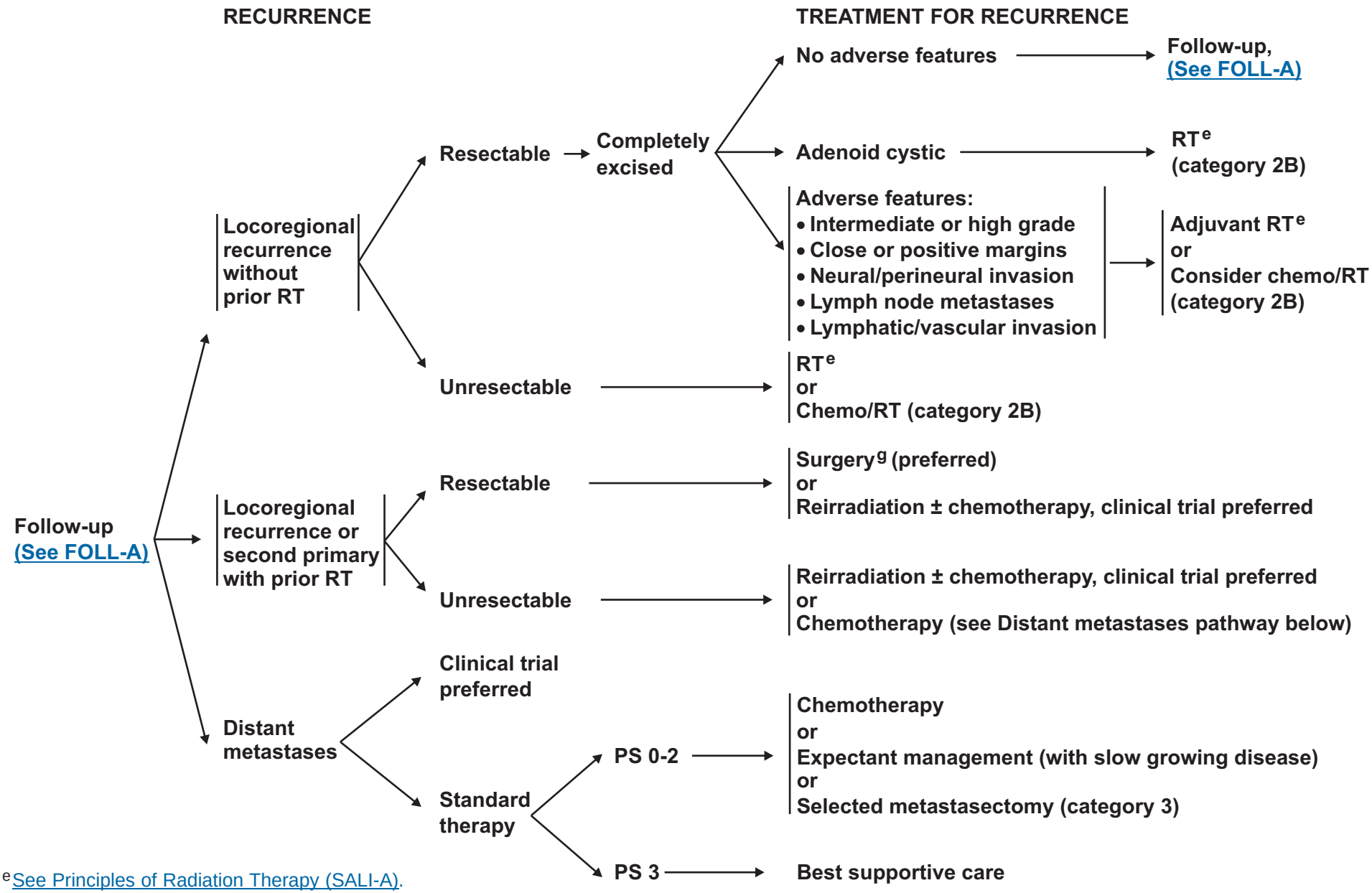


[e] See Principles of Radiation Therapy (SALI-A).
[f] The facial nerve should be preserved if possible.
[g] See Principles of Surgery (SURG-A).

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PRINCIPLES OF RADIATION THERAPY[1]

Definitive RT

T4b disease or gross residual disease

- **Photon or photon/electron therapy or neutron therapy**
- **Dose**
  - **Primary and gross adenopathy:**
    ≥ 70 Gy (1.8-2.0 Gy/fraction)[2] or
    19.2 nGy (1.2 nGy/fraction)
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)[2] or
    13.2 nGy (1.2 nGy/fraction)

Postoperative RT

- **Photon or photon/electron therapy or neutron therapy**
- **Dose**
  - **Primary: ≥ 60 Gy (1.8-2.0 Gy/fraction)[2]**
    or 18 nGy (1.2 nGy/fraction)
  - **Uninvolved nodal stations:**
    44-64 Gy (1.6-2.0 Gy/fraction)[2]
    or 13.2 nGy (1.2 nGy/fraction)

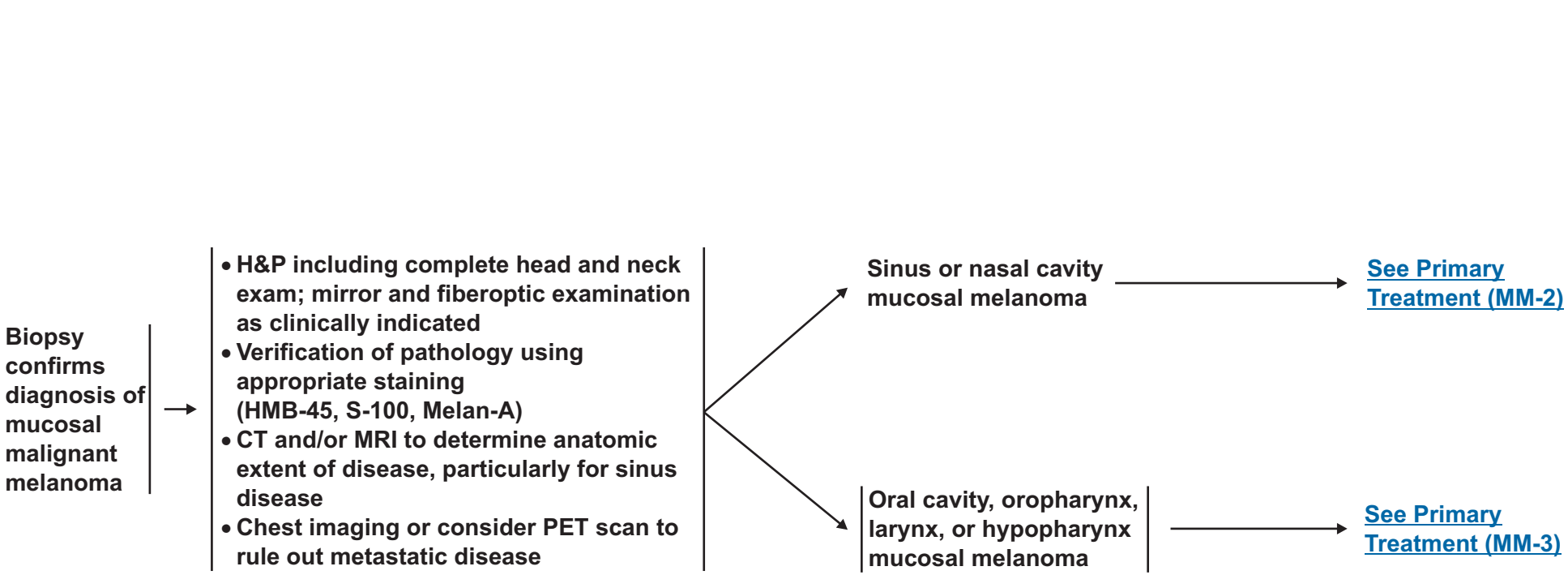
[1] See Radiation Techniques (RAD-A).

[2] Range based on grade/natural history of disease (eg, 1.8 Gy fraction may be used for slower growing tumors).

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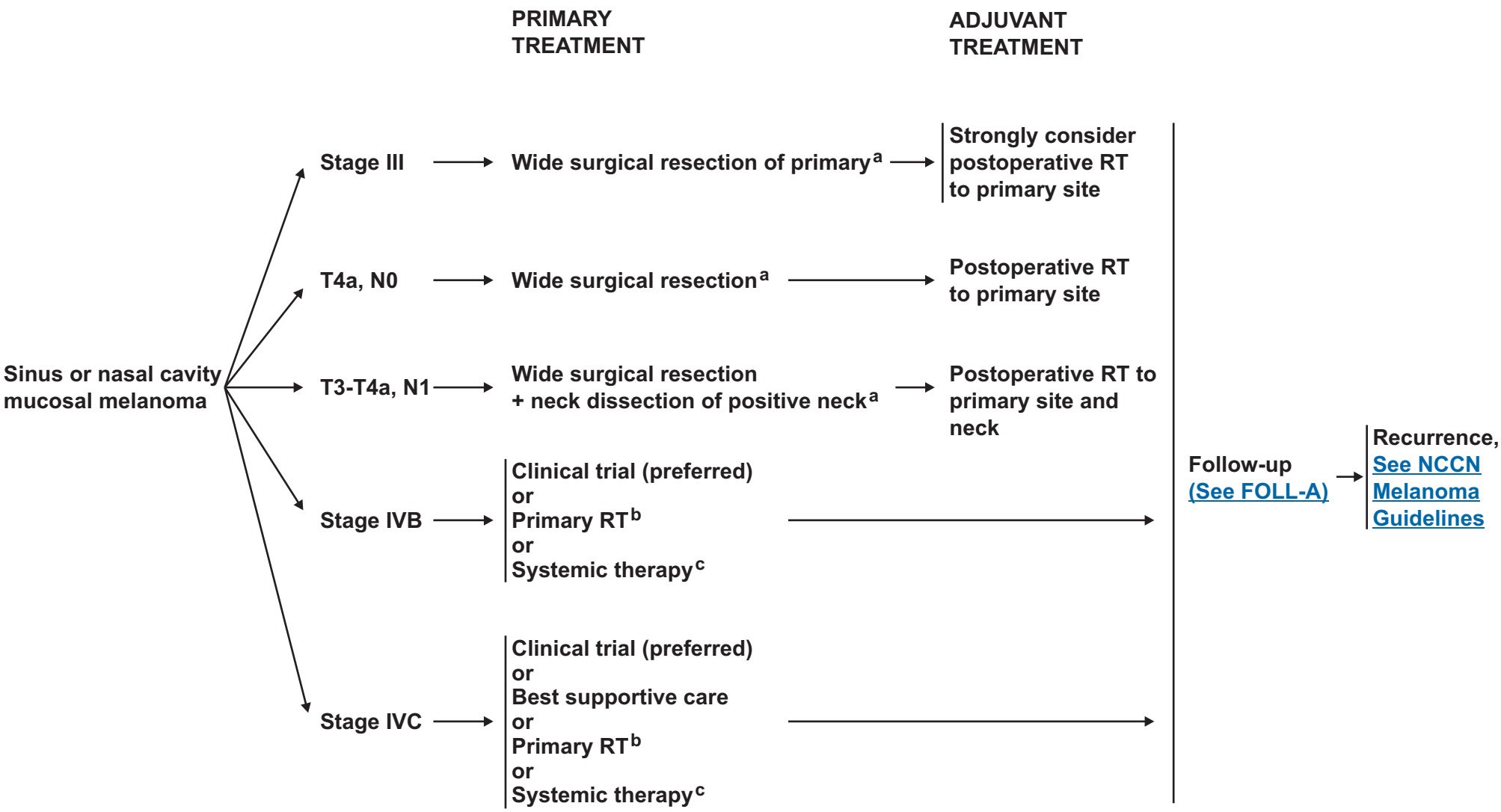
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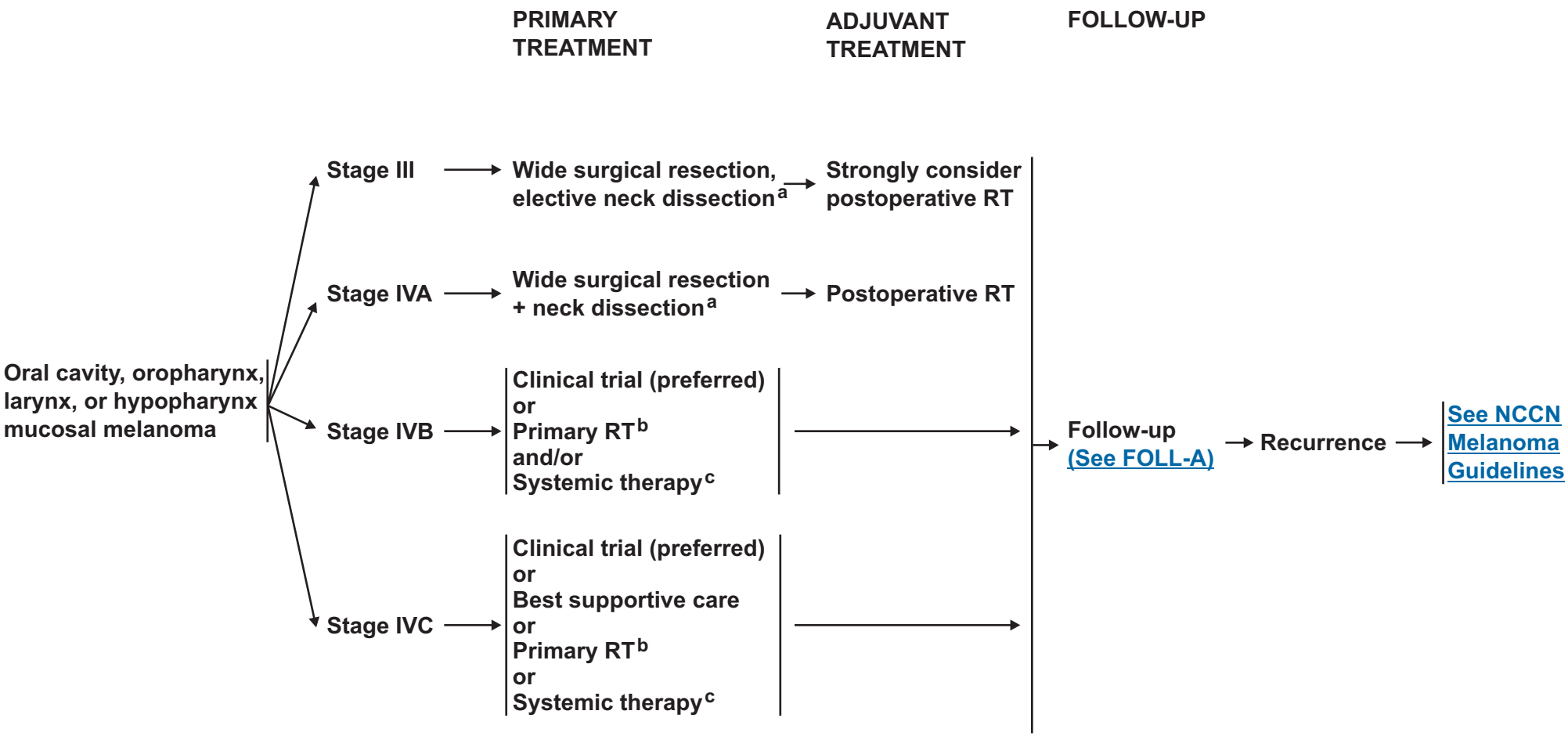


[a] See Principles of Surgery (SURG-A).
[b] See Principles of Radiation Therapy (MM-A).
[c] See Principles of Systemic Therapy for Advanced or Metastatic Melanoma page ME-D from the NCCN Melanoma Guidelines.

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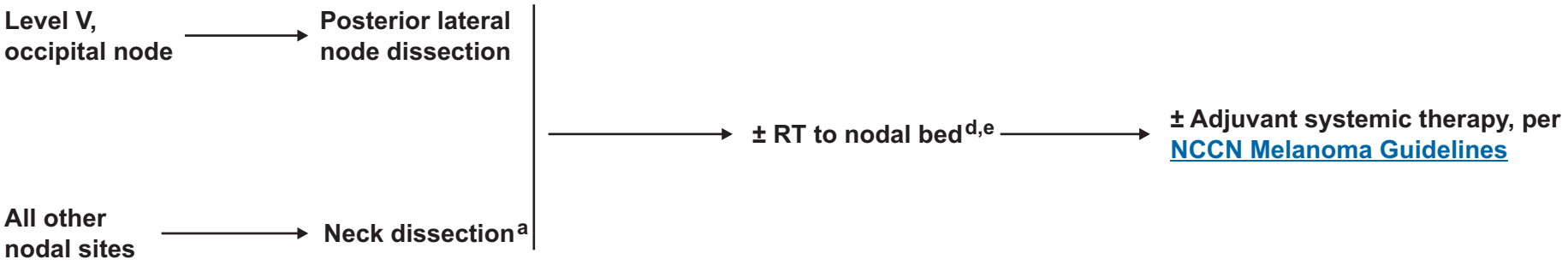
[a] See Principles of Surgery (SURG-A).
[b] See Principles of Radiation Therapy (MM-A).
[c] See Principles of Systemic Therapy for Advanced or Metastatic Melanoma page ME-D from the NCCN Melanoma Guidelines.

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PRIMARY THERAPY FOR OCCULT PRIMARY- MELANOMA



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

[d] Adjuvant radiotherapy: 30 Gy/5 fx over 2.5 weeks (6.0 Gy/fx). Careful attention to dosimetry is necessary. (Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. International Journal of Radiation Oncology, Biology, Physics 30:795-798, 1994).

[e] RT is indicated for satellitosis, positive nodes, or extracapsular spread.

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PRINCIPLES OF RADIATION THERAPY

Primary site resection:

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

Neck/nodal basin dissection:

High-risk features:

- **≥ 2 nodes**
- **Single node ≥ 3 cm**
- **Extracapsular nodal disease**
- **Node excision (alone) with no further basin dissection**
- **Recurrence in nodal basin after previous surgery.**

Dose and Fractionation:

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

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FOLLOW-UP RECOMMENDATIONS

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

[1]For mucosal melanoma, physical exam should include endoscopic inspection for paranasal sinus disease.
[2]For cancer of the oropharynx, hypopharynx, glottic larynx, supraglottic larynx, and nasopharynx: imaging recommended for T3-4 or N2-3 disease only.

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PRINCIPLES OF SURGERY

Evaluation

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

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

Integration of Therapy

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

Assessment of Resectability

Tumor involvement of the following sites is associated with poor prognosis* or with T4b cancer (ie, unresectable based on technical ability to obtain clear margins).

- **Significant involvement of pterygopalatine fossa, severe trismus due to tumor infiltration into the pterygoid muscles;**
- **Gross extension of tumor to the skull base (i.e. erosion of the pterygoid plates or sphenoid bone, widening of the foramen ovale, etc.);**
- **Direct extension to superior nasopharynx or deep extension into the Eustachian tube and lateral nasopharyngeal walls;**
- **Suspected invasion (encasement) of the common or internal carotid artery. Encasement is usually assessed radiographically and defined as tumor surrounding the carotid artery 270 degrees or greater;**
- **Direct extension of neck disease to involve the external skin;***
- **Direct extension to mediastinal structures, prevertebral fascia or cervical vertebrae.***

*In selected cases, surgery might still be considered.

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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 wide excision using accepted criteria for adequate excision, depending on the region involved.

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

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PRINCIPLES OF SURGERY

Margins

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

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

Surgical management of cranial nerves VII, X (including the recurrent laryngeal nerve), XI, and XII

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

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

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PRINCIPLES OF SURGERY

Neck Management

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

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

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

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

N0 Selective or modified radical neck dissection
-Oral cavity at least levels I-III
-Oropharynx at least levels I-IV
-Larynx at least levels II-IV and level VI when appropriate
-Hypopharynx at least levels II-IV and level VI when appropriate.
N1 Selective neck dissection or modified radical neck dissection
N2a-b Selective or modified radical neck dissection
N2c Bilateral modified (selective) radical neck dissection or combined with a unilateral selective neck dissection
N3 Modified or radical neck dissection

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

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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 surgical salvage, as well. Neck disease in an untreated neck should be addressed by formal neck dissection or modification depending on the clinical situation. Non-surgical therapy may also be utilized as clinically appropriate.

Surveillance

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

- **Tumor evaluations must be performed by specialists skilled in head and neck clinical examination.**
- **The frequency of evaluation is summarized elsewhere in the NCCN guidelines (See Follow-up Recommendations [FOLL-A]).**
- **Post chemoradiation or RT neck evaluation (See Principles of Surgery-Neck Evaluation SURG-A 6 of 6)**

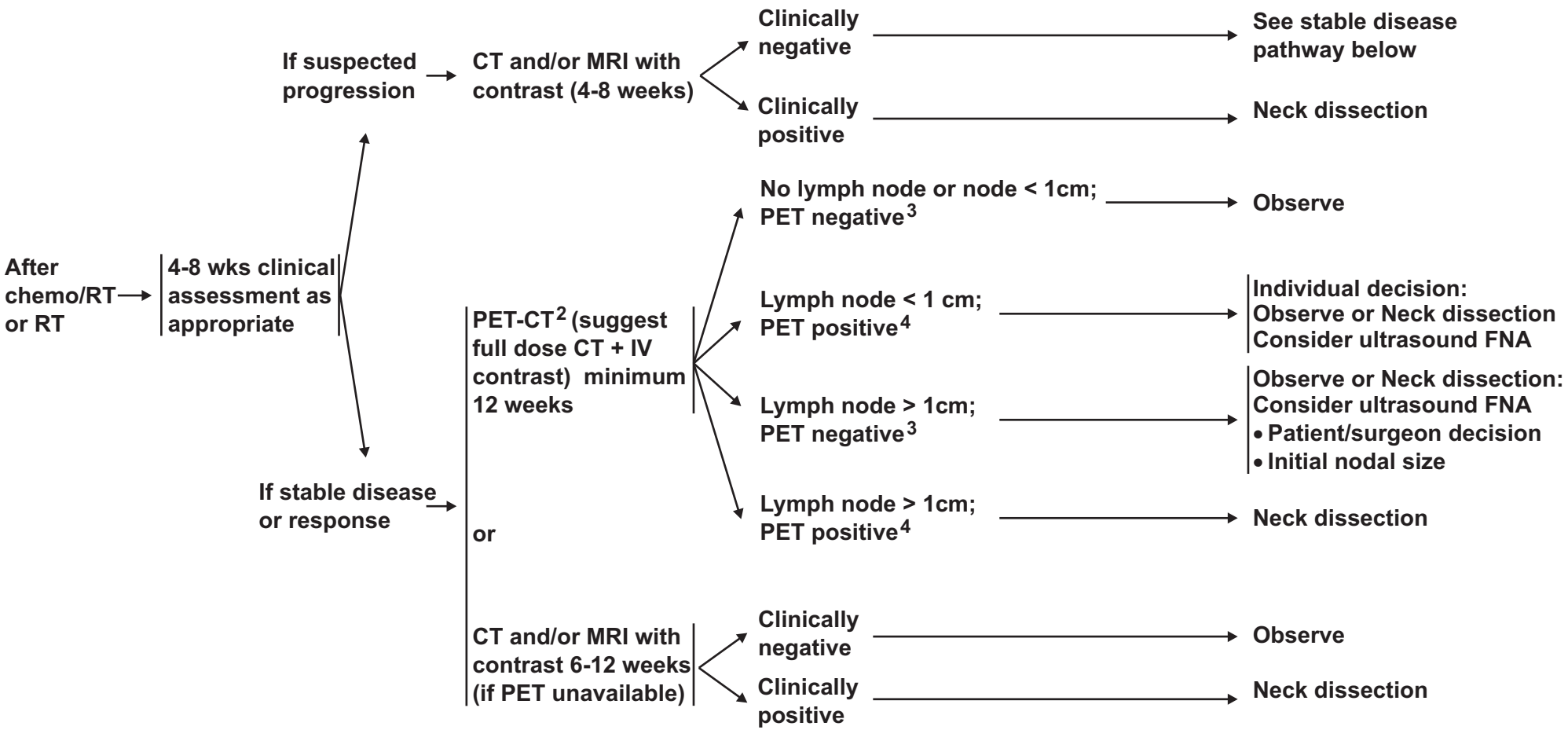
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PRINCIPLES OF SURGERY (POST CHEMORADIATION OR RT NECK EVALUATION)[1]



[1]Adapted with permission from Kutler DI, Patel SG, Shah JP.The role of neck dissection following definitive chemoradiation. Oncology 2004;18:993-998; discussion 999, 1003-4, 1007. Review
[2]If a PET-CT is performed and negative for suspicion of persistent cancer, further cross-sectional imaging is optional.
[3]PET negative = No or low-grade uptake, felt not suspicious for disease
[4]PET positive = PET suspicious for disease

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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, 3D, and 2D conformal techniques may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support. Close interplay exists between radiation technology, techniques, fractionation, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control.

Intensity-Modulated Radiotherapy (IMRT)

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

IMRT and Fractionation

A number of ways exist to integrate IMRT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (66-74 Gy to gross disease; 50-60 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation.[4] SIB is commonly used in conventional (5 fractions/week) and the "6 fractions/week accelerated" schedule.[5] The Sequential (SEQ) IMRT technique typically delivers the initial (lower dose) phase (weeks 1-5) followed by the high-dose boost volume phase (weeks 6-7) using 2-3 separate dose plans, and is commonly applied in standard fractionation and hyperfractionation. The Concomitant Boost Accelerated schedule may utilize a "Modified SEQ" dose plan by delivering the dose to the subclinical targets once a day for 6 weeks, and a separate boost dose plan as a second daily fraction for the last 12 treatment days.[6]

[1] Dogan N, King S, Emami B, et al. Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. Int J Radiat Oncol Biol Phys 2003;57(5):1480-1491.

[2] Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;66(4):966-974.

[3] Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2007;69(2):459-468. Epub 2007 May 9.

[4] Mohan R, Wu Q, Morris M, et al. "Simultaneous Integrated Boost" (SIB) IMRT of advanced head and neck squamous cell carcinomas—dosimetric analysis. Int J Radiat Oncol Biol Phys 2001;51(3):180–181.

[5] Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362(9388):933-940.

[6] Schoenfeld GO, Amdur RJ, Morris CG, et al. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;71(2):377-385. Epub 2007 Dec 31.

[7] Wolden SL, Chen WC, Pfister DG, et al. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 2006;64(1):57-62. Epub 2005 Jun 2.

[8] Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys 2000;46(1):195-205.

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PRINCIPLES OF SYSTEMIC THERAPY (Page 1 of 2)

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

Squamous Cell Cancers

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

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

Postoperative Chemoradiation
- Cisplatin alone[9-11] (category 1 for high risk)

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

Nasopharynx

Chemoradiation followed by adjuvant chemotherapy
- Cisplatin + RT followed by Cisplatin/5-FU[16] (category 1)

Recurrent, Unresectable, or Metastatic (incurable)

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

Single agents
- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- 5-FU
- Methotrexate
- Ifosfamide
- Bleomycin
- Gemcitabine[22] (nasopharyngeal)
- Cetuximab[23]

See References on page CHEM-A 2 of 2

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

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

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Staging

Table 1

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for the Lip and Oral Cavity

(7th ed., 2010)

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

Primary Tumor (T)

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

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)

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

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Staging

Table 1 - Continued

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for the Lip and Oral Cavity

(7th ed., 2010)

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

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

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

Primary Tumor (T)

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

Nasopharynx

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

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

Oropharynx

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

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

Hypopharynx

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

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

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Table 2 - Continued

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

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

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

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

Regional Lymph Nodes (N)†:
Oropharynx and Hypopharynx

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

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

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Table 2 - Continued

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

Anatomic Stage/Prognostic Groups: Nasopharynx

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

Anatomic Stage/Prognostic Groups: Oropharynx, Hypopharynx

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

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

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Table 3

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

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

Primary Tumor (T)

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

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a Moderately advanced local disease
Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4a Moderately advanced local disease
Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

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Table 3 - continued

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

Regional Lymph Nodes (N)*

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

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

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Anatomic Stage/Prognostic Groups

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

Histologic Grade (G)

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

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Table 4

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasal Cavity and Paranasal Sinuses (7th ed., 2010)

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

Primary Tumor (T)

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

Maxillary Sinus

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

Nasal Cavity and Ethmoid Sinus

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

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Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

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Table 4 - Continued

American Joint Committee on Cancer (AJCC)

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

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

Anatomic Stage/Prognostic Groups

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

Histologic Grade (G)

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

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Table 5

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

Primary Tumor (T)

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

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

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

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Table 6

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

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

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

Histologic Grade (G)

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

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

The NCCN Head and Neck (H&N) Cancers guidelines address tumors arising in the lip, oral cavity, pharynx, larynx, paranasal sinuses, and salivary glands (see Figure 1); occult primary cancer and mucosal melanoma are also addressed.[1] A brief overview of the epidemiology and management of H&N cancer is provided.

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

Incidence and Etiology

It is estimated that about 49,260 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur in 2010, which accounts for about 3% of new cancer cases in the United States. An estimated 11,480 deaths from H&N cancers will occur in 2010.[2] 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 cancer are at risk for developing second primary neoplasms of the H&N, lung, esophagus, and other sites that share these risk factors.

Human papillomavirus (HPV) infection is now well accepted as a risk factor for the development of squamous cancers of the oropharynx (predominately cancers of the lingual and palatine tonsils).[3-9] The overall incidence of HPV positive H&N cancer is increasing in the United States, while the incidence of HPV negative (primarily tobacco- and alcohol-related) cancer is decreasing.[10] A strong causal relationship has been established between the HPV type 16 and development of oropharyngeal cancer (see HPV in the oropharyngeal section).[3]

Staging

Stage at diagnosis predicts survival rates and guides management in patients with H&N cancer. The 2010 American Joint Committee on Cancer (AJCC) staging classification (7th edition) was used as a basis for the NCCN's treatment recommendations for H&N cancer.[11,12] The 7th edition of the AJCC staging guidelines became effective January 1, 2010.[11] The AJCC added a new staging table for mucosal melanoma in the 7th edition, which is described below (see Table 6). However, no major changes in the T classification or stage groupings for the other sites have been made in the revisions for the 7th edition for H&N cancer; the minor changes are described below.

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The TNM staging systems developed by the AJCC for the lip and oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx (glottis and supraglottis), paranasal sinuses (ethmoid and maxillary), major salivary glands (parotid, submandibular, and sublingual), and mucosal melanoma are shown in Tables 1, 2, 3, 4, 5, and 6 respectively.[12] Definitions for regional lymph node (N) involvement and spread to distant metastatic sites (M) are uniform except for N staging of nasopharyngeal carcinoma (see Table 2). Definitions for staging the primary tumor (T), based on its size, are uniform for the lip, oral cavity, and oropharynx. In contrast, T stage is based on subsite involvement and is specific to each subsite for the glottic larynx, supraglottic larynx, hypopharynx, and nasopharynx.

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

The anatomic criteria for definitions of T4a and T4b for the oropharynx, hypopharynx, larynx, nasal cavity, paranasal sinuses, and major salivary glands remain unchanged in the 7th edition of the AJCC staging manual. However, the words “resectable” (T4a) and “unresectable” (T4b) have been replaced by the terms “moderately advanced” (T4a) and “very advanced” (T4b). These changes were deemed necessary, because a substantial proportion of advanced stage malignancies of the H&N, although resectable, are being treated non-surgically. Furthermore, a clear consensus in criteria for resectability can be difficult to obtain. For example, some tumors deemed inoperable are anatomically resectable; however, surgery is not pursued because of medical contraindications to surgery or because it is anticipated that surgery will not improve prognosis. Therefore, the terms “resectable” and “unresectable” were deemed inappropriate for selection of therapy. This change in terminology allows revising of stage IV disease into moderately advanced local/regional disease (stage IVA), very advanced local/regional disease (stage IVB), and distant metastatic disease (stage IVC) for many sites (i.e., lip, oral cavity, oropharynx, hypopharynx, larynx, paranasal sinuses, major salivary glands, and mucosal melanoma).

A new algorithm for mucosal melanoma was added to the 2010 NCCN H&N guidelines, which includes the new AJCC staging table (see Table 6). Mucosal melanomas are rare, very aggressive tumors that mainly affect the nasal cavity and paranasal sinuses. Thus, melanomas confined to the mucosa only are T3; those with moderately advanced lesions (involving underlying cartilage or bone) are T4a, and very advanced primary tumors are T4b.

Minor changes have been made in the T staging categories for the nasopharynx (see Table 2). Thus, T2a lesions will now be designated T1; therefore, former stage IIA is now stage I. Lesions previously staged T2b will be T2; therefore, former stage IIB is now stage II. Regardless of unilateral or bilateral location, retropharyngeal lymph nodes are considered N1.

Management Approaches

Treating the patient with H&N cancer is complex. The specific site of disease, the extent of disease (stage), and the pathologic findings guide the appropriate surgical procedure, radiation targets, dose and fractionation, and indications for chemotherapy. Single-modality treatment with surgery or radiotherapy is generally recommended for the approximately 30%-40% of patients who present with early-stage disease (stage I or stage II). The 2 modalities result in similar survival in these individuals. In contrast, combined modality therapy is generally

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recommended for the 60% of patients with locally or regionally advanced disease at diagnosis.

Participation in clinical trials is a preferred or recommended treatment option, particularly for patients with locally or regionally advanced disease. In formulating these H&N guidelines, the panel has tried to make them evidence based while providing a statement of consensus as to the acceptable range of treatment options.

Multidisciplinary Team Involvement

The initial evaluation and development of a plan for treating the patient with H&N cancer require a multidisciplinary team of health care providers with expertise in caring for these patients. Similarly, managing and preventing sequelae of radical surgery, radiotherapy, and chemotherapy (e.g., pain, xerostomia, speech and swallowing problems, depression) require professionals familiar with the disease. Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help to prevent severe weight loss in patients receiving treatment for H&N cancer; therefore, patients should be encouraged to see a dietician.[13] Patients should also be encouraged to stop smoking and to modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes.[14,15] Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA [Food and Drug Administration]) can be very useful (http://www.ahrq.gov/path/tobacco.htm). Specific components of patient support and follow-up are listed in the algorithm (see TEAM-1). The panel also recommends referring to the NCCN Guidelines for Palliative Care.

Comorbidity and Quality of Life

Comorbidity

Comorbidity refers to the presence of concomitant disease (in addition to H&N cancer) that may affect the diagnosis, treatment, and prognosis for the patient.[16-18] Documentation of comorbidity is particularly important in oncology, to prevent inaccurate attribution of poor outcomes to the cancer. Comorbidity is known to be a strong independent predictor for mortality in H&N cancer patients,[18-25] and comorbidity also influences costs of care, utilization, and quality of life.[26-28] Traditional indices of comorbidity include the Charlson index[17] and the Kaplan-Feinstein index and its modifications.[18,29] The Adult Comorbidity Evaluation-27 (ACE-27) is specific for H&N cancer and has excellent emerging reliability and validity.[30,31]

Quality of Life

Health-related quality-of-life issues are paramount in H&N cancer. These tumors affect basic physiological functions (i.e., the ability to chew, swallow, and breathe), the senses (taste, smell, and hearing), and uniquely human characteristics (i.e., appearance and voice). *Health status* describes an individual's physical, emotional, and social capabilities and limitations. *Function* and *performance* refer to how well an individual is able to perform important roles, tasks, or activities. *Quality of life* differs, because the central focus is on the *value* (determined by the patient alone) that individuals place on their health status and function.[32] A National Institutes of Health (NIH)–sponsored conference[33] recommended the use of patient-completed scales to measure quality of life. For H&N cancer-specific issues, the 3 validated measures that have received the most widespread acceptance are: (1) the University of Washington Quality of Life scale (UW-QOL);[34] (2) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35);[35] and (3) the Functional Assessment of Cancer Therapy Head and Neck module (FACT-HN).[36]

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The Performance Status Scale for H&N cancer patients is a clinician-rated performance scale—with a narrower focus than the previously mentioned Quality of Life scales—that has also achieved widespread use.[37]

Head and Neck Surgery

Principles of Surgery

A new section on "Principles of Surgery" was added to the 2010 NCCN H&N guidelines (see SURG-A).[1] Evaluation, integration of therapy, assessment of resectability, primary tumor resection, margins, surgical management of cranial nerves (VII, X-XII), neck management, management of recurrences, and surveillance (including post-treatment neck evaluation) are discussed in the Principles of Surgery. All patients should be evaluated by a H&N surgical oncologist before treatment. In addition, it is critical that multidisciplinary evaluation and treatment be coordinated and integrated prospectively by specialists from all the modalities involved in patient care.

The various site-specific sections of these H&N guidelines primarily pertain to patients for whom surgery is a treatment option. The treatment of patients with locally advanced T4b or unresectable nodal disease, metastatic disease, or recurrent disease is addressed in the "Very Advanced/Recurrent/Persistent Head and Neck Cancers" section of these guidelines (see ADV-1). The following represents a brief summary of the new Principles of Surgery.

The resection of advanced tumors of the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinus varies in extent depending on the structures involved. To be deemed "resectable," the primary tumor should be considered surgically curable by wide excision using accepted criteria for adequate excision, depending on the region involved. Frozen section margin assessment 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 (i.e., base of/anterior tongue, mandible, larynx, part of the cervical esophagus). 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.

The surgical management of the regional lymphatics is dictated by the extent of tumor at initial tumor staging. In general, patients having surgical resection of the primary tumor will have neck dissection of the ipsilateral neck that is at greatest risk for metastases. Patients with advanced lesions involving the anterior tongue or floor of the mouth which approximate or cross the midline, should have contralateral submandibular dissection as necessary to achieve adequate tumor resection.

Neck disease in an untreated neck should be addressed by formal neck dissection or modification, depending on the clinical situation; nonsurgical therapy may also be used as clinically appropriate. The NCCN Neck Evaluation algorithm can be used to assess whether neck dissection is recommended after chemoradiation or RT (see SURG-A 6).[38] All patients should have regular follow-up visits after surgery to assess for symptoms and possible tumor recurrence, health behaviors, nutrition, dental health, and speech & swallowing defects.

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 cancer are treated. The NCCN member institutions have teams experienced in the treatment of H&N cancer and maintain the multidisciplinary infrastructure needed for

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reconstruction and rehabilitation. A patient's cancer is deemed unresectable if H&N surgeons at NCCN member institutions do not think they can remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after an operation (even with the addition of radiotherapy to the treatment approach). Typically, these unresectable tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery (see SURG-A 1). Tumor involvement of certain sites is associated with poor prognosis (i.e., direct extension of neck disease to involve the external skin, direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae).

Unresectable tumors (i.e., 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 these tumors should not be deemed unresectable. Although local and regional disease may be surgically treatable, patients with distant metastases are usually treated as though the primary tumor was unresectable. Thus, patient choice or a physician's expectations regarding cure and morbidity will influence or determine treatment.

Patients with resectable tumors who can also be adequately treated without surgery represent a very important group. Definitive treatment with radiation therapy (RT) alone or RT combined with chemotherapy may represent equivalent or preferable approaches to resection in these individuals. Although such patients may not undergo surgery, their tumors should not be labeled as unresectable. Their disease is usually far less extensive than disease that truly cannot be removed. Because a substantial number of patients with advanced stage malignancies of the H&N are being treated non-surgically, the terms "resectable" (T4a) and "unresectable" (T4b) are no longer used in the new staging for H&N cancers (see Tables 1-6).[11] These terms have been replaced by "moderately advanced" (T4a) and "very advanced" (T4b).

Neck Dissection

Historically, cervical lymph node (i.e., neck) dissections have been classified as "radical" or "modified radical" procedures. The less radical procedures preserved the sternocleidomastoid muscle, jugular vein, and spinal accessory nerve. The panel prefers to classify cervical lymphadenectomy using contemporary nomenclature and, thus, classifying cervical lymph node dissections as either "comprehensive" or "selective."

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

Selective neck dissections have been developed based on an understanding of the common pathways for spread of H&N cancers to regional nodes (see Figure 2).[39,40] A supraomohyoid neck dissection removes the nodes most commonly involved with metastases from the oral cavity. A supraomohyoid neck dissection includes nodes found above the omohyoid muscle (levels I-III and the superior parts of level V). Similarly, a lateral neck dissection removes the nodes most commonly involved with metastases from the pharynx and larynx. A lateral neck dissection includes nodes in levels II-IV (see SURG-A). 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).[41-43] The chief role of neck dissections in these NCCN H&N guidelines is to select patients for

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possible adjuvant radiotherapy, although selective neck dissections may be used as treatment when neck tumor burden is low.[44] In general, patients undergoing selective neck dissection should not have clinical nodal disease.[45] In the guidelines, patients with cervical node metastases who undergo operations with therapeutic intent are generally treated with comprehensive neck dissections, because often they have disease outside the bounds of selective neck dissections.

In patients who appear to have a complete clinical response or stable disease after either RT or chemoradiation, post-treatment evaluation with imaging (i.e., CT and/or MRI with contrast, PET-CT,) can be used to guide use of neck dissection (see SURG-A).[46-49] If PET is used for follow-up, the first scan should be performed at approximately 12 weeks after treatment to increase sensitivity and to reduce the false-positive rate.[47,50]

Note that a *complete clinical response* (i.e., clinically negative) may be defined as no visible or palpable neck disease and no radiographic findings (i.e., the absence of either focally abnormal lymph nodes or large nodes (> 1.5 cm).[46,51] A complete pathologic response includes pathologic confirmation. If a complete response has been achieved in patients who were N0 at initial staging, all of the panel members recommend observing the patient (see HYPO-3, ORPH-4, and other sites).[46,51,52] In patients who have a clinically negative neck, a negative PET/CT is 90% reliable and further imaging is optional.[53-55] Patients with an excellent (but less than complete) nodal response (e.g., residual nodal mass in the 1.5-2.5 cm range) may benefit from PET/CT to evaluate for metabolic activity and need for neck dissection. Panelists also concur that any patient with residual disease in the neck after radiotherapy or chemoradiation should undergo a neck dissection.[46]

Postoperative Management of High-Risk Disease

Many factors influence survival and locoregional tumor control in patients with H&N cancer. In most NCCN member institutions, patients with extracapsular nodal spread and/or positive surgical margins receive adjuvant chemoradiotherapy after resection.[56-61] The presence of other adverse risk factors—multiple positive nodes (without extracapsular nodal spread), vascular/lymphatic/perineural invasion, pT3 or pT4 primary, and oral cavity or oropharynx primary cancers with positive level 4 or 5 nodes—are established indications for postoperative RT. Because patients with these other adverse features were also included in the European trial that showed a survival advantage for patients receiving cisplatin concurrent with postoperative radiotherapy compared to radiotherapy alone (i.e., the European Organization for Research and Treatment of Cancer [EORTC] 22931 trial), the panel added “consider chemoradiation” for these features.[62]

The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has been clarified by 2 separate multicenter randomized trials[62,63] and a combined analysis of data from the 2 trials for patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx.[64] The US Intergroup trial—the Radiation Therapy Oncology Group (RTOG) 95-01 trial —randomly assigned patients with 2 or more involved nodes, positive margins, or extracapsular spread of tumor to receive standard postoperative radiotherapy or the same radiotherapy plus cisplatin 100 mg/m^2 every 3 weeks for 3 doses.[63] The EORTC 22931 trial was designed using the same treatment but also included as high-risk factors the presence of perineural or perivascular disease and nodal involvement at levels 4 and 5 from an oral cavity or oropharynx cancer.[62] The RTOG trial demonstrated statistically significant improvement in locoregional control and disease-free survival but not overall survival, whereas the EORTC trial found significant improvement in survival and the other outcome parameters. Both the RTOG and EORTC trials use high-dose

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cisplatin (100 mg/m^2 every 3 weeks). A schedule using cisplatin at 50 mg IV weekly has also demonstrated improved survival in this setting in a randomized trial.[65]

To better define risk, a combined analysis of prognostic factors and outcome from the 2 trials was performed. This analysis demonstrated that patients in both trials with extracapsular nodal spread of tumor and/or positive resection margins benefited from the addition of cisplatin to postoperative radiotherapy. For those with multiple involved regional nodes without extracapsular spread, there was no survival advantage.[64] The NCCN panel noted that the combined analysis was considered exploratory by the authors, because it was not part of the initial protocol design.[64] These publications form the basis for the NCCN recommendations.

Head and Neck Radiotherapy

In the 2010 NCCN H&N guidelines, the radiotherapy guidelines were revised for each site (see UPDATES). Radiotherapy for H&N cancer has grown increasingly complex. The availability and technical precision of intensity modulated radiotherapy has markedly increased, perhaps beyond our confidence in estimating location of small subsites of microscopic disease. A thorough understanding of natural history, anatomy, clinical circumstances, and imaging continue to guide the use of radiation as primary treatment or as an adjuvant. The NCCN radiotherapeutic guidelines are not all inclusive. Although technical guidelines are rapidly evolving and becoming more specific, advanced technologies provide much opportunity for variations and individualization in targeting and dose delivery, challenging traditional notions of “standard” fields and targets.

Radiation Doses

Selection of radiation total dose depends on the primary tumor and neck node size, fractionation, and clinical circumstances, including whether to use concurrent chemotherapy (see RAD-A and individual guidelines for each site [e.g., HYPO-A]). In general, primary tumor and gross adenopathy require a total of 66-74 Gy, and up to 81.6 Gy in hyperfractionation. External radiation doses exceeding 75 Gy using conventional fractionation (1.8 to 2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury.

In contrast, elective irradiation to low and intermediate risk nodal stations in the neck requires 44-64 Gy, depending on estimated level of tumor burden, fraction size, and use of chemotherapy. Postoperative irradiation is recommended based on stage, histology, and surgical-pathological findings. In general, postoperative RT to 50-60 Gy is recommended for selected risk factors, including advanced T-stage, close margins, depth of invasion, multiple positive nodes (without extracapsular nodal spread), or perineural/lymphatic/vascular invasion. Higher doses of radiation alone (60-66 Gy), or with chemotherapy, are recommended for the high-risk features of extracapsular disease and positive margins. The preferred interval between resection and commencement of postoperative RT is 6 weeks or less.

Fractionation in RT Alone

No single fractionation schedule has proven to be best for all tumors. Data strongly indicate squamous cancers of the H&N can grow rapidly, and may compensate for radiotherapy-induced cell loss through the mechanism of accelerated repopulation.[66-68] Schedules delivering at least 1000 cGy per week, especially in RT alone settings, are recommended, with the exception of salivary gland tumors, which may have slower cell kinetics.[69-73] Trials in early-stage glottic larynx cancer have shown higher recurrence rates with daily fraction sizes <200 cGy where the cumulative weekly dose is <1000 cGy.[74,75]

Two large, randomized clinical trials from Europe have reported improved locoregional control using altered fractionation. The EORTC

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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, there was a statistically significant increase in local control in the hyperfractionation arm (38% versus 56%; *P*=.01) and no increase in late complications.[76] A long-term follow-up analysis has also demonstrated a small survival advantage for hyperfractionation (*P*=.05).[77] 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.[78]

The RTOG reported the initial 2-year results and subsequent mature results (after a median follow-up of 8.5 years) of a 4-armed phase III randomized clinical trial (protocol 90-03) comparing hyperfractionation and 2 variants of accelerated fractionation against standard fractionation.[79,80] After 2 years of follow-up, both accelerated fractionation with a concomitant boost (AFX-C) and hyperfractionation were associated with improved locoregional control and disease-free survival compared with standard fractionation. However, acute toxicity was increased. No significant difference was demonstrated in the frequency of grade 3 or worse late effects reported at 6 to 24 months after treatment start, among the various treatment groups. Long-term follow-up confirmed a statistically significant improvement in locoregional control with either AFX-C or hyperfractionation compared to standard fractionation. However, neither disease-free survival nor overall survival were significantly improved.

A meta-analysis of updated individual patient data from 15 randomized trials analyzing the effect of hyperfractionated or accelerated radiotherapy on survival of patients with H&N cancer has been published.[81] Standard fractionation constituted the control arm in all of the trials in this meta-analysis. An absolute survival benefit of 3.4% at 5 years (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.[81] 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.[80-83]

Fractionation in Concurrent Chemoradiation

There is no consensus regarding the optimal radiation dose fractionation scheme when administered with concurrent chemotherapy. Most published studies have used conventional fractionation at 2.0 Gy per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m^2. Use of other fraction sizes (e.g., 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated. Numerous trials have shown that modified fractionation and concurrent chemotherapy are more efficacious than modified fractionation alone.[83-86] However, whether modified fractionation and concurrent chemotherapy is superior to standard fractionation and concurrent chemotherapy is unknown at this time.

Concurrent chemoradiation increases acute toxicity compared to radiation alone, although an increase in late toxicity beyond that caused by radiotherapy alone is less clear.[87-89] Altered fractionation and/or multiagent chemotherapy may further increase the toxicity burden.[90] For any chemotherapeutic approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and

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schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

Radiation Techniques and IMRT

The intensity of the radiation beam can be modulated in order to decrease doses to normal structures without compromising the doses to the cancer targets. Intensity-modulated radiation therapy (IMRT) is an advanced form of conformal RT permitting more precise cancer targeting while reducing dose to normal tissues.[91-94] Xerostomia is a common long-term side effect of RT, which can be reduced with use of IMRT, drug therapy (e.g., pilocarpine, cevimeline), and other novel approaches (e.g., acupuncture).[95-99]

IMRT dose painting refers to the method of assigning different dose levels to different structures within the same treatment fraction (e.g., 2.0 to gross tumor, 1.7 to microscopic tumor, and <1.0 Gy to parotid gland) resulting in different total doses to different targets (e.g., 70 Gy, 56 Gy, <26Gy).[100] Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can occur.[100,101] 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 RAD-A).[93,102]

IMRT is now widely used in H&N cancer and is the predominant technique used at NCCN centers. 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.[95,96,103-109] However, overall survival is similar between patients treated with IMRT and those receiving conventional RT.[103,110,111] In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT.[112,113] The application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians.[114,115]

Numerous phase II studies show a decrease in late toxicity (xerostomia) without compromising tumor control for nasopharyngeal, sinonasal, and other sites. More recently, 3 randomized trials have supported the clinical benefits of IMRT in H&N cancer. Pow and colleagues evaluated treatment of early-stage nasopharyngeal carcinoma with conventional radiotherapy techniques versus with IMRT.[95] The results showed a statistical improvement in salivary flow and in patient-reported quality of life parameters.[95] In the study by Kam and colleagues, patients with nasopharyngeal carcinoma were randomized to either IMRT or conventional 2-D radiotherapy.[96] At 1 year after treatment, patients in the IMRT arm had significantly lower rates of clinician-rated severe xerostomia than patients in the 2-D RT arm (39.3% versus 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.

The PARSPORT phase III trial has reported preliminary findings at ASCO 2009 in the non-nasopharyngeal carcinoma setting.[116] In this trial, patients with T1-T4, N0-N3, M0 disease were treated to a total dose of 65 Gy in 30 fractions either with parallel opposed technique or with IMRT; 80 patients with oropharyngeal and 14 patients with hypopharyngeal tumors were included. Grade 2 or greater (LENT-SOMA scale) xerostomia 1 year after treatment was seen in 74% of patients receiving conventional treatment versus 40% of patients in the

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IMRT group. No differences were seen in the rates of locoregional control rates or survival.

Follow-up After RT

For patients whose cancer has been treated with RT, the recommended follow-up (see FOLL-A) includes an assessment of thyroid function (i.e., the thyroid stimulating hormone [TSH] level should be determined every 6 to 12 months). Increased TSH levels have been detected in 20% to 25% of patients who received neck irradiation.[117]

Brachytherapy

Brachytherapy is used less often in recent years because of improved local control obtained with concurrent chemoradiation. However, brachytherapy still has a role for lip cancer (see LIP-A).[118]

Cancer of the Lip

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

Workup and Staging

The workup for patients with squamous cell carcinoma of the lip consists of a complete H&N examination and other appropriate studies (see LIP-1). A dental Panorex (panoramic x-ray) and computerized tomographic (CT) scan or magnetic resonance imaging (MRI) are done if bone invasion is suspected. The AJCC TNM staging system reflects tumor size, extension, and nodal disease (see Table 1). This system does predict the risk for local recurrence. The location of the primary tumor also is predictive. Tumors in the upper lip and commissural areas have a higher incidence of lymph node metastases at the time of diagnosis. Systemic dissemination is rare, occurring in approximately 10% to 15% of patients, most often in those with uncontrolled locoregional disease.

Treatment of the Primary

The treatment of lip cancer is governed by the stage of the disease. The choice of a local treatment modality is based on the expected functional and cosmetic outcome. In early-stage cancers (T1-2, N0), surgery is preferred and radiation is an option in terms of local control (see LIP-2).[119-121] Some very small or superficial cancers are managed more expeditiously with a surgical excision without resultant functional deformity or an undesired cosmetic result. A superficial cancer that occupies most of the lower lip, however, would be best managed with RT.[122] 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 the local modality of choice for advanced cancers with extension into the bone. Patients with resectable T3-,T4a, N0; or any T, N1-3 disease who are a poor surgical risk can be treated with definitive RT (with or without brachytherapy) or with chemotherapy/RT.[122] 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 LIP-4).

Management of the Neck

The management of the neck is also governed by stage, but the location of the tumor should also be taken into account. For example,

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the lymphatics of the upper lip are very extensive. Thus, tumors in this location are more apt to spread to deep superior jugular nodes. The position of the tumor along the lip also can be helpful in predicting the pattern of lymph node spread. A midline location can place a patient at higher risk for contralateral disease. For patients with advanced disease (T3, T4a) and an N0 neck, a unilateral or bilateral selective neck dissection is recommended (see LIP-3). When a patient presents with palpable disease, care is taken to ensure all appropriate nodal levels are dissected.

Radiation

Radiotherapy, when used as definitive treatment, may consist of external-beam RT with or without brachytherapy, depending on the size of the tumor. The dose required also depends on tumor size, but doses of 66 Gy or more are adequate to control the disease. For T1-2, N0 lesions, the total dose of external-beam RT may be 50-66 Gy (see LIP-A). In the adjuvant setting, doses of 60 Gy or more are required, depending on the pathologic features. In both definitive and adjuvant settings, the neck is treated with doses that address adverse features, such as positive margins or invasion (perineural, vascular, and/or lymphatic).[123]

Follow-up/Surveillance

Recommendations are provided in the algorithm (see FOLL-A).

Cancer of the Oral Cavity

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

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

Workup and Staging

Imaging studies to evaluate mandibular involvement and a careful dental evaluation (including Panorex, as indicated) are particularly important for staging (see Table 1) and planning therapy for oral cavity cancers in addition to a complete H&N examination, biopsy, and other appropriate studies (see OR-1).

Treatment

Surgery and RT represent the standards of care for early-stage and locally advanced resectable lesions in the oral cavity. The specific treatment is dictated by the TN stage and, if N0 at diagnosis, by the risk of nodal involvement (see OR-2). Multidisciplinary team involvement is particularly important for this site because of the critical physiologic functions of mastication, deglutition, and articulation of speech, which may be affected. Most panelists prefer surgical therapy for resectable oral cavity tumors. Advances in reconstruction using microvascular techniques have led to improved functional outcomes for patients with locally advanced disease.

Postoperative chemotherapy/RT (preferred) or re-excision of positive margins (if technically feasible) is recommended (category 1 for both) for all patients with resected oral cavity cancers with the adverse pathologic features of extracapsular nodal spread and/or a positive mucosal margin.[62-64] Primary RT may be offered to selected patients

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who are medically inoperable or refuse surgery. For other risk features—such as pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, selected pT2 N0-1 disease, or perineural invasion or vascular embolism—clinical judgment should be utilized in the consideration of adding chemotherapy to RT or treating with RT alone. The concept of organ preservation using chemotherapy in the initial management of locally advanced resectable disease has received less attention in the management of oral cavity cancers, because the functional outcome after primary surgical management is often quite good.

Follow-up/Surveillance

Recommendations are provided in the algorithm (see FOLL-A).

Cancer of the Oropharynx

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

Workup and Staging

A multidisciplinary consultation is encouraged. Accurate staging depends on complete H&N examination coupled with appropriate imaging studies (see ORPH-1).[124] Examination of the H&N region should include an examination under anesthesia with endoscopy.

HPV Testing

A number of studies have recently documented a rising incidence of HPV-related cancer, now estimated to comprise up to 60% to 70% of newly diagnosed cancers of the oropharynx in the United States and parts of the European Union.[10,125,126] A strong causal relationship has been established between HPV type 16 and development of oropharynx cancer.[3] Prospective and retrospective analyses of clinical trials indicate that patients with HPV-positive cancers have improved response to treatment and improved survival and progression-free survival when compared with HPV-negative tumors.[127-131] How this information should be used in routine clinical decision-making and in the design of clinical trials is currently a matter of intense investigation among NCCN centers. There is growing consensus that HPV status should be used as a stratification factor or should be addressed in separate trials (HPV related versus unrelated) for which oropharynx patients are eligible.

With the exception of cancers of unknown primary (see next paragraph), the panel believes that HPV status should not be a routine consideration in treatment selection at this time. Additional studies are needed to better understand the effect of HPV status on response to different therapies, treatment outcome, and patterns of failure and in relation to other prognostic or predictive factors such as smoking history and stage. A number of clinical trial groups are reporting retrospective analyses of response to therapy in HPV-related versus HPV-unrelated oropharynx cancers.[127,128,130] The panel strongly urges that, where available, patients with HPV-related cancers be enrolled in clinical trials evaluating biological and treatment-related questions.

HPV testing can be useful in workup and management of cancers of the neck of unknown primary. An HPV-positive test strongly suggests an occult primary is located in the tonsil or base of tongue regions, suggesting one may choose to limit radiation targets to these mucosal regions.[132]

HPV testing options in a clinical setting include HPV in situ hybridization [ISH]) and a surrogate marker, p16 immunohistochemistry (which is a more widely available test that has been shown in several studies to strongly correlate with HPV status and is associated with improved

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prognosis).[128-130] The panel notes that HPV testing may prompt questions about prognosis (i.e., a favorable, or a less favorable forecast) and sexual history that the clinician should be prepared to address. Thus, without a specific reason for testing, HPV information may add anxiety and stress for some patients. Alternatively, gaining an understanding of the etiology for one's cancer can result in reduced anxiety for some patients.

Treatment

The treatment algorithm has been divided into 3 staging categories: (1) T1-2, N0-1; (2) T3-4a, N0-1; and (3) any T, N2-3. T4b, N any, or unresectable nodal disease is treated as advanced cancer (see ADV-1). Early-stage (T1-2, N0-1) oropharyngeal cancers may be treated with primary surgery including neck dissection, as indicated, or with definitive radiotherapy. The panel members felt that the third option of RT plus systemic therapy (category 2B for systemic therapy) was only appropriate for T2, N1 (see ORPH-2). Adjuvant chemotherapy/RT is recommended (category 1) for adverse pathologic features of extracapsular nodal spread and/or positive mucosal margin.[62-64]

For locally advanced resectable disease (T3-4a, N0-1), there are 3 treatment approaches in the algorithms (see ORPH-3), in addition to enrollment in a multimodality clinical trial that includes function evaluation. The 3 approaches are: (1) concurrent systemic therapy/RT cisplatin (category 1) preferred (salvage surgery is used for managing residual or recurrent disease);[87] (2) surgery with appropriate radiation-based adjuvant therapy; or (3) induction chemotherapy followed by RT or chemo/RT (category 3) for which there was major disagreement among panel members (see next section).[87,133-137]

Concurrent systemic therapy/RT with cisplatin alone (category 1) is preferred for treatment of locally or regionally advanced (T3-4a, N0-1, or any T, N2-3) cancer of the oropharynx. Panel members differed in their opinion as to whether induction chemotherapy should be considered a standard treatment option for T3-4a, N0-1 disease. This disagreement is reflected by a category 3 recommendation in the algorithms. There are insufficient data at the present time to customize treatment selection by tumor HPV status.

The Induction-Sequential Chemotherapy Controversy

The use of induction chemotherapy added to concurrent chemoradiotherapy (termed sequential therapy) remains an area of controversy among the NCCN panel members. Most randomized trials of induction chemotherapy followed by radiotherapy or surgery (published in the 1980s and 1990s) did not demonstrate a survival advantage.[138] Induction chemotherapy had no effect on local control; however, in some trials, it did reduce the distant metastatic rate.[139] A rationale for reevaluating induction chemotherapy added to concurrent chemotherapy/RT is to determine whether or not it reduces distant metastases as a site of failure now that improved local control can be achieved with concurrent chemotherapy/RT.

Results from 3 phase III trials—which compared induction cisplatin plus infusional 5-fluorouracil (5-FU) with or without the addition of a taxane (docetaxel or paclitaxel) followed by the same locoregional treatment—showed significantly improved outcomes (response rates, disease-free survival, or overall survival depending on the trial) for patients in the 3-drug induction group compared to those receiving 2 drugs (cisplatin plus 5-FU).[135,137,140] Taken together, these results show that a more effective triplet combination has been identified compared to the standard of cisplatin plus 5-FU used in the induction trials of the 1980s and 1990s. However, a survival advantage from the addition of induction chemotherapy to concurrent chemoradiation has yet to be demonstrated. A recent meta-analysis of 93 randomized trials also reported that concomitant chemotherapy was more beneficial than

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induction chemotherapy.[141] However, the analysis did not include more recent studies containing taxane-based induction.[137,140]

The issue concerning induction chemotherapy remains uncertain in part, because it is not yet clear which patients are best suited for induction chemoradiation. Furthermore, although docetaxel, cisplatin, and 5-FU (TPF) presently is the most extensively studied induction regimen, there remains considerable uncertainty and disagreement concerning which chemoradiation plan should follow it. Panel members agree that high-dose cisplatin (100 mg/m^2 every 21 days x 3) may not be feasible in this setting. There is no one preferred regimen to use. Panel members agreed that many different approaches, including concurrent low-dose weekly cisplatin, weekly taxanes, cetuximab, or combinations thereof are reasonable, but inadequately studied, to be specifically recommended. Some panel members specifically considered exclusive use of low-dose weekly carboplatin in this setting to be inadequate. Because of this uncertainty, clinical trial enrollment of patients in this setting is particularly encouraged.

The issues regarding induction have become even more challenging as new data emerge. Two studies reported at ASCO 2009 suggest that compliance with high-dose platinum concurrent with radiation can be problematic after induction therapy using TPF.[142,143] Other sequential induction-concurrent regimens, using less aggressive induction or less intensive concurrent chemotherapy, appear to have higher compliance rates.[137,144] However, a definitive study has not been done comparing these newer strategies to concurrent chemoradiotherapy alone.

Neck Dissection After Chemoradiation

For the concurrent systemic therapy/RT approach, all patients are evaluated at completion of treatment for response in the primary site and in the neck. For patients with nodal involvement at initial staging who achieve a complete clinical response in the primary and the neck, subsequent management is based on initial nodal stage. Patients who had N0-1 disease are observed, while patients who had N2 or N3 disease can be either observed or undergo a planned neck dissection, depending on the results of post-treatment evaluation (see SURG-A).

Radiation Therapy Fractionation

Standard conventional fractionation is preferred when radiotherapy is used definitively for T1-2, N0 tumors. Altered fractionation is appropriate for selected T1-2, N1 tumors, particularly if concurrent chemotherapy is not used. The recommended schedules are shown on ORPH-A. The RTOG 9003 fractionation study indicated a local control advantage for patients who were treated with hyperfractionation and concomitant boost versus those treated with standard fractionation or accelerated fractionation with a break in the treatment schedule.[79,80] Increased acute toxicity was demonstrated in both altered fractionation schedules when compared with standard radiotherapy. The concomitant boost schedule resulted in prolongation of acute symptoms 6 to 24 months after the initiation of treatment, but no significant difference was demonstrated in the frequency of late effects among schedules. In addition to the RTOG 9003 trial, 3 other randomized trials and a recent meta-analysis have confirmed improved outcomes with several forms of altered fractionation.[76,78,81,145]

Fractionation in Concurrent Chemoradiation

There is no consensus regarding the optimal radiation dose fractionation scheme when administered with concurrent chemotherapy. Most published studies have used conventional fractionation at 2.0 Gy per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m^2. Use of other fraction sizes (e.g., 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated. Numerous trials have shown that modified fractionation and concurrent chemotherapy is more efficacious than modified fractionation alone.[83-86]

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However, whether modified fractionation and concurrent chemotherapy is superior to standard fractionation and concurrent chemotherapy is unknown. Currently, we are waiting for results of RTOG 0129 which tests this question in the setting of concurrent cisplatin.[128]

Concurrent chemoradiation increases acute toxicity compared to radiation alone, although an increase in late toxicity beyond that caused by radiotherapy alone is less clear.[87-89] Altered fractionation and/or multiagent chemotherapy may further increase the toxicity burden.[90] 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.

Salvage Surgery

Patients with advanced carcinoma of the oropharynx (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 ORPH-4). The patients who do not have a complete clinical response to chemotherapy/RT require salvage surgery plus neck dissection as indicated. However, all panelists emphasized that it may be difficult to detect local or regional recurrence due to radiation-related tissue changes, and this may result in a delayed diagnosis of persistent or recurrent disease.

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

Follow-up/Surveillance

Recommendations are provided in the algorithm (see FOLL-A).

Cancer of the Hypopharynx

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

Workup and Staging

A multidisciplinary consultation is encouraged. Accurate staging (see Table 2) depends on a complete H&N examination coupled with appropriate studies (see HYPO-1).

At the time of diagnosis, approximately 60% of patients with cancer of the hypopharynx have locally advanced disease with spread to regional nodes. Furthermore, autopsy series have shown a high rate of distant metastases (60%) involving virtually every organ.[146] Thus, the prognosis for patients with cancer of the hypopharynx is quite poor. Despite standard radical surgery and radiotherapy, the persistent or recurrent locoregional disease and distant dissemination contribute to the poor outcome for these patients.

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Treatment

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

Patients with more advanced disease (defined as T1, N+; T2-3, any N) requiring total laryngectomy and partial or total pharyngectomy may be managed with 3 approaches (see HYPO-3) in addition to enrollment in a multimodality clinical trials: (1) induction chemotherapy followed by definitive RT if a complete response was achieved at the primary site (category 1)[147] or followed by other options depending on the response (see HYPO-4); (2) surgery with neck dissection and postoperative radiation or chemoradiation as dictated by pathologic risk features; or (3) concurrent chemotherapy/RT cisplatin preferred. The standard induction regimen for option 1 is now TPF based on the results of recent randomized trials.[137,140,148] Given the functional loss resulting from this surgery and the poor prognosis, participation in clinical trials is emphasized.

The recommendation of the induction chemotherapy /definitive radiotherapy option is based on the results of an EORTC randomized trial.[147] This trial enrolled 194 eligible patients with stage II, stage III, or stage IV resectable squamous cell carcinoma of the pyriform sinus (152 patients) and aryepiglottic fold (42 patients), excluding patients with T1 or N2c disease. Patients were randomly assigned either to laryngopharyngectomy and postoperative radiotherapy, or to chemotherapy with cisplatin and 5-FU for a maximum of 3 cycles, followed by definitive radiotherapy. In contrast to a similar approach used for laryngeal cancer, a complete response to induction chemotherapy was required in order to proceed with definitive radiotherapy. The published results showed equivalent survival, with median survival duration and 3-year survival rate of 25 months and 43%, respectively, for the surgery group versus 44 months and 57%, respectively, for the induction chemotherapy group.[147] A functioning larynx was preserved in 42% of patients who did not undergo surgery. Local or regional failure rates did not differ between the surgery-treated patients and chemotherapy-treated patients, although the chemotherapy recipients did demonstrate a significant reduction in distant metastases as a site of first failure (P=.041). Adherence to the requirements for complete response to chemotherapy and for inclusion of only patients with the specified TN-stage are emphasized. These results were recently confirmed in a randomized phase III trial with 450 patients; the median overall survival was 4.4 years.[149] 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.[148]

As noted in the algorithm, surgery is recommended if less than a partial response occurs after 3 cycles of induction chemotherapy (see HYPO-4). In this situation, or when primary surgery is the selected management path, postoperative chemotherapy/RT is recommended (category 1) for adverse pathologic features of extracapsular nodal spread and/or positive mucosal margin. For other risk features, clinical judgment should be utilized when deciding to use RT alone or when considering adding chemotherapy to RT (see HYPO-3).

Options for patients with T4a, any N disease (see HYPO-5) include surgery plus neck dissection (preferred) followed by adjuvant chemotherapy/RT or RT, multimodality clinical trials, or category 3 recommendations.

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Follow-up/Surveillance

Recommendations are provided in the algorithm (see FOLL-A). It is particularly important for nonsurgically treated patients to have careful and regular follow-up examinations by a trained H&N surgical oncologist so that any local or regional recurrence is detected early, and salvage surgery (and neck dissection as indicated) is performed.

Cancer of the Nasopharynx

Carcinoma of the nasopharynx is uncommon in the United States. Among H&N cancers, it has the highest propensity to metastasize to distant sites. Nasopharyngeal cancer also poses a significant risk for isolated local recurrences after definitive radiation (without chemotherapy) for locally advanced disease.[150-153] Regional recurrences are uncommon in this disease, occurring in only 10% to 19% of patients.[153,154]

The NCCN H&N guidelines for the evaluation and management of carcinoma of the nasopharynx attempt to address risk for both local and distant disease. Stage is accepted as prognostically important. The prognostic significance of histology is still controversial. RT was the standard treatment for all stages of this disease, until the mid-1990s, when trial data showed improved survival for locally advanced tumors treated with concurrent RT and cisplatin.[155]

Workup and Staging

The workup of nasopharyngeal cancer includes a complete H&N examination and other studies (see NASO-1). These studies are important to determine the full extent of tumor in order to assign stage appropriately and to design radiation ports that will encompass all the disease with appropriate doses. Multidisciplinary consultation is encouraged. The 2010 AJCC staging classification is used as the basis for treatment recommendations (see Table 2). For patients with WHO class 2-3/N2-3 disease, imaging for distant metastases (i.e., chest, liver, bone) may include PET scan and/or CT.

Treatment

Treatment options are subdivided according to T, N, and M status, rather than by stage alone. Patients with early-stage nasopharyngeal tumors (T1, N0, M0) may be treated with definitive RT alone (see NASO-1). For early-stage cancer, radiation doses of at least 70 Gy given with standard fractions are necessary for control of gross tumor (see NASO-A). The local control rate for these tumors ranges from 80% to 90%, whereas T3-4 tumors have a control rate of 30% to 65%.[156,157]

The combination of RT and platinum-based chemotherapy has been shown to increase the local control rate from 54% to 78%. The Intergroup trial 0099, which randomly assigned patients to chemotherapy plus external-beam RT versus external radiation alone, closed early when an interim analysis disclosed a significant survival and progression-free survival advantage favoring the combined chemotherapy and radiation group.[155] The addition of chemotherapy also decreased local, regional, and distant recurrence rates. A similar randomized study conducted in Singapore, which was modeled after the Intergroup treatment regimen, continued to show the benefit of the addition of chemotherapy to radiation therapy. Adjuvant chemotherapy after combined chemotherapy and radiation was also given in this trial.[158] In addition, the administration of the cisplatin dose was spread out over several days, and this regimen appeared to reduce toxicity while still providing a beneficial antitumor effect.

The guidelines recommend combined chemotherapy (cisplatin) plus radiotherapy (category 1) for T1, N1-3; and for T2-T4, any N lesions (see NASO-2). The scheduling and doses of chemotherapy are those used in the intergroup trial 0099.[155] Although an unusual occurrence, a patient with residual disease in the neck and a complete response at

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the primary should undergo a neck dissection. Initial therapy for patients who present with metastatic disease should consist of a platinum-based combination chemotherapy regimen. Commonly used active agents alone or in combination include gemcitabine, paclitaxel, cisplatin, or carboplatin.[159-163] Likewise, cetuximab plus carboplatin may be useful for patients with recurrent or metastatic nasopharyngeal cancer who have failed platinum-based therapy. Gemcitabine monotherapy or in combination with cisplatin may also be useful.[161-163]

Follow-up/Surveillance

Recommendations are provided in the algorithm (see FOLL-A).

Cancer of the Larynx

The larynx is divided into 3 regions: supraglottis, glottis, and subglottis. The distribution of cancers is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region, and 5% in the subglottic region. The AJCC staging classification for laryngeal primary tumors is determined by the number of subsites involved, vocal cord mobility, and the presence of metastases (see Table 3).

The incidence and pattern of metastatic spread to regional nodes varies with the primary region. More than 50% of patients with supraglottic primaries present with spread to regional nodes because of an abundant lymphatic network that crosses the midline. Bilateral adenopathy is not uncommon with early-stage primaries. Thus, supraglottic cancer is often locally advanced at diagnosis. In contrast, the lymphatic drainage of the glottis is sparse and early-stage primaries rarely spread to regional nodes. Because hoarseness is an early symptom, most glottic cancers are in an early stage at diagnosis. Thus, glottic cancers have an excellent cure rate—in the range of 80% to 90%. As with other cancers of the H&N, nodal involvement decreases survival rates by approximately 50%.

Workup and Staging

The evaluation of the patient to determine tumor stage is similar for glottic and supraglottic primaries (see GLOT-1 and SUPRA-1). CT, MRI, or PET/CT imaging tests are considered particularly important for accurate staging. Multidisciplinary consultation is critical for both sites because of the potential for loss of speech and, in some instances, for swallowing dysfunction.

Treatment

The treatment of patients with laryngeal cancer is divided into 3 categories: (1) tumors of the glottic larynx, (2) tumors of the supraglottic larynx without positive nodes (N0), and (3) tumors of the supraglottic larynx with positive nodes (N+).

For patients with carcinoma in situ of the larynx, recommended treatment options include endoscopic removal (stripping, laser) or RT. For early-stage glottic or supraglottic cancers, surgery (partial laryngectomy through either endoscopic or open approaches) and radiotherapy are equally effective (see GLOT-2 and SUPRA-2). The choice of treatment modality depends on functional outcome, the patient's wishes, reliability of follow-up, and general medical condition.

Management of the neck is dictated by the risk of occult nodal spread. Resectable, advanced-stage supraglottic and glottic primaries can be managed with a combined modality approach (see SUPRA-6 and GLOT-4).[164] In patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is preferred (category 1) to induction chemotherapy for laryngeal preservation and locoregional control.[164] Selected cases can be managed with conservation surgical techniques that preserve vocal function.

Patients with locally advanced disease who desire laryngeal preservation should receive treatment with concurrent chemotherapy

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(consisting of cisplatin 100 mg/m^2 on days 1, 22, and 43 preferred) and radiotherapy (category 1 for cisplatin);[164] the second option is definitive RT (without chemotherapy) for patients who are medically unfit or refuse chemotherapy (see SUPRA-5). Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after radiotherapy, or those patients who develop a subsequent locoregional recurrence. For patients who were initially node positive and who have a complete response, post-treatment evaluation can be used to assess neck nodes.

The NCCN recommendations for managing locally advanced, resectable glottic and supraglottic cancers requiring laryngectomy reflect the results of Intergroup trial R91-11.[164] Before 2002, either induction chemotherapy with cisplatin/5-FU followed by radiotherapy or definitive radiotherapy alone (without chemotherapy) were the standard of care options recommended in the NCCN H&N guidelines based on the results of the Veterans Administration (VA) Laryngeal Cancer Study Group trial published in 1991.[165] Currently, concurrent radiotherapy and cisplatin 100 mg/m^2 is the recommended option for achieving laryngeal preservation. R91-11 was a successor trial to the Veterans Administration trial and compared 3 non-surgical regimens: (1) induction cisplatin/5-FU followed by RT (control arm and identical to that in the VA trial); (2) concurrent RT and cisplatin 100 mg/m^2 days 1, 22, and 43; and (3) RT alone. Radiotherapy was uniform in all 3 arms, 70 Gy/7 weeks, 2 Gy/fraction. Laryngectomy was used for salvage of treatment failures in all arms. Stage III and IV (M0) patients were eligible, excluding T1 primaries and high-volume T4 primaries (tumor extending more than 1 cm into the base of tongue or tumor penetrating through cartilage). The key findings of the trial were a statistically significant higher 2-year laryngeal preservation (local control) rate for concurrent RT with cisplatin of 88%, compared to 74% with induction chemotherapy and to 69% with RT alone; no significant difference in laryngeal preservation between induction and RT alone treatments; and similar survival for all treatment groups. These R91-11 results changed the standard of care to concurrent RT and cisplatin (category 1) preferred for achieving laryngeal preservation for T3, N0 and T4a, N0 supraglottic cancers and for most T3, any N glottic cancers.[164]

For patients with glottic T4a tumors, the standard approach is a laryngectomy with ipsilateral thyroidectomy and neck dissection as indicated (see GLOT-6). For selected patients with glottic T4a tumors who decline surgery, the panel recommends (1) considering concurrent chemoradiation; (2) clinical trials; or (3) induction chemotherapy followed by chemo/RT (category 2B).

For managing T4a, N0 supraglottic primaries, the recommended option is laryngectomy, ipsilateral thyroidectomy with neck dissection; adjuvant therapy depends on the risk features (see SUPRA-8). In these patients who decline surgery, concurrent chemoradiation can be considered; induction chemotherapy is also an option (category 2B).[164]

Follow-up/Surveillance

Recommendations are provided in the algorithm (see FOLL-A). It is particularly important for nonsurgically treated patients to have careful and regular follow-up examinations by a trained H&N surgical oncologist so that any local or regional recurrence is detected early, and salvage surgery (and neck dissection as indicated) is performed. Follow-up examinations in many of these patients need to be supplemented with serial endoscopy or high-resolution, advanced radiologic imaging techniques because of the scarring, edema, and fibrosis that occur in the laryngeal tissues and neck after high-dose radiation.

Paranasal Tumors (Maxillary and Ethmoid Sinus Tumors)

Tumors of the paranasal sinuses are rare and often asymptomatic until late in the course of their disease. Tumors of the maxillary sinus tumors

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are more common than those of the ethmoid sinus or nasal cavity.[11] 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), sarcoma, and undifferentiated carcinoma (sinonasal undifferentiated carcinoma [SNUC], small cell neuroendocrine).[166-169] Locoregional control and incidence of distant metastasis are dependent on T stage, N stage, and tumor histology.[170] However, T stage remains the most reliable predictor of survival and local regional control (see Table 4).

Management of Ethmoid Sinus Cancer

Patients with early-stage cancer of the ethmoid sinus 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 excision of the residual tumor. This procedure often entails an anterior craniofacial resection to remove the cribriform plate and to ensure clear surgical margins. Most patients affected by ethmoid sinus cancer present after having had an incomplete excision. The patient who is diagnosed after incomplete excision (e.g., polypectomy, endoscopic surgical procedure)—and has no documented residual disease on physical examination, imaging, and/or endoscopy—should be treated in a similar fashion if feasible (see ETHM-2). If no adverse pathologic factors are found, this treatment ensures clear surgical margins and obviates the need for postoperative radiotherapy in T1 patients only (category 2B). However, RT may be used as definitive treatment in patients if pre-biopsy imaging studies and nasal endoscopy demonstrate that the superior extent of the disease does not involve the skull base. Systemic therapy should be part of the overall treatment for patients with SNUC, esthesioneuroblastomas, or small cell neuroendocrine histologies.[171-176] Long-term follow-up is necessary for esthesioneuroblastomas, because recurrence can even occur after 15 years.[174,177]

Treatment of Maxillary Sinus Tumors

Complete surgical resection for all T stages (except T4b, any N) followed by postoperative therapy remains a cornerstone of treatment for maxillary sinus tumors (see MAXI-3).[178-181] Note that *Ohngren's line* runs from the medial cantus 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 supra-structure.

Recent studies using IMRT have shown that it reduces the incidence of late complications, such as radiation-induced ophthalmologic toxicity; however, the 5-year overall survival rate has not improved.[108,180,182,183] Participation in clinical trials is favored for patients with malignant tumors of the paranasal sinuses.

Follow-up

Recommendations are provided in the algorithm (see FOLL-A).

Very Advanced Head and Neck Cancers

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

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Treatment

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

Newly Diagnosed Advanced Disease

For patients with a performance status (PS) of 0 or 1, the standard treatment of newly diagnosed, very advanced disease is concurrent cisplatin (single agent) chemotherapy and radiotherapy (category 1).[184] The panel had a major disagreement regarding whether induction chemotherapy (TPF) followed by chemoradiation should be used for patients with a PS of 0 or 1, which is reflected in the category 3 recommendation (see ADV-1).[137,140] Other options are described in the algorithm (see ADV-1).

Many randomized trials[65,85,86,184-190] and meta-analyses of clinical trials[138,191-194] demonstrate significantly improved overall survival, disease-free survival, and local control when a concomitant or alternating chemotherapy and radiation regimen is compared with radiotherapy alone for advanced disease. All combined chemoradiotherapy regimens are associated with various degrees of enhanced mucosal toxicities, which require close patient monitoring, ideally provided by a team experienced in treating H&N cancer patients. Limited data are available comparing the efficacy of different chemoradiotherapy regimens. Therefore, no optimal standard chemoradiation regimen is defined. Single-agent cisplatin plus RT is effective and relatively easy to administer and typically uses conventional fractionation at 2.0 g per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m^2 (see ADV-A).[184]

Bonner and colleagues randomly assigned 424 patients with locally advanced and measurable stage III/IV squamous cell carcinomas of the H&N to receive definitive radiotherapy with or without cetuximab.[195] Locoregional control and median overall survival (49 months versus 29.3 months, *P*=.03) were significantly improved in patients treated with radiotherapy and cetuximab compared to radiotherapy alone. Radiotherapy and cetuximab may provide a therapeutic option for patients not considered medically fit for standard chemoradiotherapy regimens. Other preferential chemoradiation options were also identified by the panel (see CHEM-A).[196,197] Limited data are available comparing combination chemoradiation versus using a single agent concurrently with RT.

Recurrent or Persistent Disease

Surgery is recommended for resectable recurrent or persistent locoregional disease; adjuvant therapy depends on the risk factors (see ADV-2). If the recurrence is unresectable and the patient did not have prior RT, then radiotherapy with concurrent systemic therapy is recommended, depending on the PS (see ADV-1). For patients with recurrent disease not amenable to curative-intent radiation or surgery, the treatment approach is the same as that for patients with metastatic disease; enrollment in a clinical trial is preferred. A randomized phase III trial in patients with metastatic or recurrent H&N cancer found no significant difference in survival when comparing cisplatin plus 5-FU with cisplatin plus paclitaxel.[198] Other combination regimens used in this patient population include carboplatin plus 5-FU[199] and cetuximab plus cisplatin.[200,201] Cetuximab can also be added to cisplatin or carboplatin plus 5-FU and is described in greater detail below.[202] These regimens are all listed as treatment options for this patient population (see CHEM-A).

Squamous cell carcinomas emerge after the accumulation of multiple genomic events. In a multistep process, there appear to be essential molecular alterations, which confer a survival advantage for cancer cells. The epidermal growth factor receptor (EGFR) is a trans-membrane glycoprotein; activation of EGFR triggers a cascade of

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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 (i.e., erlotinib and gefitinib).

Data from phase II studies indicate that in the cisplatin-refractory setting, the single-agent response rate of cetuximab is about 12% to 14%. Burtness and colleagues[200] compared cisplatin plus cetuximab versus cisplatin plus placebo as first-line treatment of recurrent disease; they reported a significant improvement in response rate with cetuximab (26% versus 10%, respectively). Of note, a phase III randomized trial (EXTREME) of 442 patients with recurrent or metastatic squamous cell carcinoma found that cetuximab plus cisplatin/5-FU or carboplatin/ 5-FU improved median survival when compared to the standard chemotherapy doublet (10.1 months versus 7.4 months, *P*=.04).[202] The response rate was also improved with cetuximab (20% to 36% [*P*<.001]).

Metastatic Disease

Palliative adjunctive measures include radiotherapy to areas of symptomatic disease, analgesics, and investigational agents aimed at controlling locally advanced tumors. Single agents and combination systemic chemotherapy regimens are both used (see CHEM-A). Response rates to single agents range from 15% to 35%. The most active single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, ifosfamide, bleomycin, gemcitabine (for nasopharyngeal cancer), and cetuximab.[161,203-205] Active combination regimens include (1) cisplatin or carboplatin, plus 5-FU[198,199] with cetuximab[202]; (2) cisplatin or carboplatin, plus a taxane;[198,206] or (3) cisplatin with cetuximab.[200] These regimens result in response rates of 30% to 40%.

Randomized trials assessing a combination of cisplatin plus 5-FU versus single-agent therapy with cisplatin, 5-FU, or methotrexate have demonstrated significantly higher response rates for the combination regimen. No difference in overall survival, however, is demonstrable.[198,199,207-209] The median survival with chemotherapy is approximately 6 months, and the 1-year survival rate is approximately 20%. Achievement of a complete response is associated with longer survival and, although infrequent, has been reported more often with combination regimens.[199]

The standard treatment of patients with incurable, recurrent, or metastatic H&N cancer should be dictated, in large part, by the patient's PS (see ADV-2). Patients should be fully informed about the goals of treatment, cost of combination chemotherapy, and potential for added toxicity.

Occult Primary Cancer

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

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

Workup

When patients present with a neck mass, they should have a complete H&N examination (including examination of the nasopharynx, oropharynx, larynx, and hypopharynx; attention to the skin; and nasopharyngoscopy). Fine-needle aspiration (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 thoroughly apprised of treatment decisions and related sequelae.

When a needle biopsy demonstrates squamous cell carcinoma, adenocarcinoma, or anaplastic epithelial cancer and no primary site has been found, additional studies are needed (see OCC-1). A PET/CT scan should only be done (before biopsy) if other tests do not reveal a primary. PET can be used to confirm clinical impressions, detect an unknown primary, and for surveillance.

HPV-16 and Epstein Barr Virus (EBV) testing are suggested for squamous cell or undifferentiated histology.[161,210-213] HPV testing can be useful in workup and management of cancers of the neck of unknown primary. An HPV-positive test strongly suggests an occult primary is located in the tonsil or base of tongue regions, permitting one to limit radiation targets to these mucosal regions.[132]

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 clinical significance of such tumors is uncertain. When patients have been treated without tonsillectomy and the therapeutic benefit of this surgery, only a few develop a clinically significant primary tumor.

Treatment

Neck dissection is recommended for all patients with thyroglobulin-negative adenocarcinoma (see OCC-2). If the metastatic adenocarcinoma presents high in the neck, parotidectomy may be included with the neck dissection. After neck dissection, management depends on the findings (ie, N1 without extracapsular spread, N2 or N3 without extracapsular spread, or extracapsular spread) (see OCC-4, OCC-5, or OCC-6).

NCCN member institutions have major disagreements about the management of patients with squamous cell carcinoma, poorly differentiated or nonkeratinizing squamous cell, anaplastic cancer (not thyroid) of unknown primary site, or other uncommon histologies. Some members believe such patients should be managed with comprehensive neck dissection (levels I-V), whereas others believe the following options can be used (most are category 3): (1) chemoradiation (category 2B); (2) primary RT; or (3) induction chemotherapy followed by chemoradiation or RT (see OCC-3).

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After a neck dissection, most NCCN institutions recommend radiation that encompasses the potential primary sites as determined by the neck node levels involved for N1 disease without extracapsular spread (see OCC-4). Postoperative radiation or concurrent chemoradiation (category 2B for chemoradiation) is recommended for N2 or N3 disease without extracapsular spread (see OCC-5). Although some NCCN institutions would radiate the neck only (category 3), most institutions would also radiate the likely occult primary sites based on the level of nodes involved. Extending the radiation field to encompass all possible mucosal primary sites is controversial and the source of much disagreement. Little evidence supports a survival benefit from radiation to all possible primary sites. For extracapsular spread, concurrent chemoradiation is a category 1 recommendation (see OCC-6).[62,63]

Salivary Gland Tumors

Salivary gland tumors can arise in the major salivary glands (parotid, submandibular, sublingual) or in one of the minor salivary glands, which are widely spread throughout the aerodigestive tract.[214] Many minor salivary gland tumors are located on the hard palate. Approximately 20% of the parotid gland tumors are malignant; the incidence of malignancy in submandibular and minor salivary gland tumors is approximately 50% and 80%, respectively. These malignant tumors constitute a broad spectrum of histologic types, including mucoepidermoid, acinic, adenocarcinoma, adenoid cystic carcinoma, malignant myoepithelial tumors, and squamous carcinoma. The primary diagnosis of squamous carcinoma of the parotid gland is rare; however, the parotid is a frequent site of metastasis from skin cancer.[215] Prognosis and tendency to metastasize vary among these histologic types. Major prognostic factors are histologic grade, tumor size, and local invasion (see Table 5).

Treatment

The major therapeutic approach for salivary gland tumors is adequate and appropriate surgical resection.[216-218] Surgical intervention requires careful planning and execution, particularly in parotid tumor surgery because the facial nerve is in the gland, which should be preserved if the nerve is not directly involved by the tumor. Most parotid gland tumors are located in the superficial lobe, and if the facial nerve is functioning preoperatively, the nerve can be preserved in most patients. 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 where the patient may require superficial parotidectomy and identification and retraction of the facial nerve to remove the deep lobe parotid tumor.

Most malignant deep lobe parotid tumors will require postoperative RT because of adverse features such as the limitations of surgical margins in the resection of these tumors (see SALI-A). RT is also used in an adjuvant setting for tumors with other adverse features (e.g., intermediate or high grade);[216] chemotherapy/RT (category 2B) can also be considered (see SALI-3). Cisplatin has been used as a radiosensitizer at other sites, but there are limited data for salivary gland tumors. The panel was not in agreement regarding chemoradiation, because there are limited published trials of this approach for unresectable salivary gland tumors. Chemotherapy may be used for palliation in advanced disease. Various agents (e.g., cisplatin, cyclophosphamide, doxorubicin, mitoxantrone; carboplatin and vinorelbine) and combinations of these have been shown in small series to be active for some salivary gland malignant histologies.[219-221]

Follow-up

Recommendations are provided in the algorithm (see FOLL-A).

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Mucosal Melanoma of the Head and Neck

Mucosal melanoma (MM) is a rare but highly aggressive neoplasm with a poor prognosis. It may occur throughout the upper aerodigestive tract. Most MM (70%-80%) occurs in the nasal cavity or paranasal sinus region, and most of the remainder develops in the oral cavity.[222] Sinonasal MM is typically confined to the primary site at presentation.[223] Oral cavity MM more frequently presents with clinically apparent lymph node metastasis.[224] No etiological risk factors are yet apparent.

Staging and Workup

The AJCC Cancer Staging Manual (7th edition) now includes the first staging system for MM (see Table 6);[11] previous editions have not had a classification for MM. The new staging recognizes 2 key factors specific to MM: 1) the poor prognosis of the disease 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 it breaks the disease down into stages reflecting local burden of disease, as well as regional and distant extent. In addition, the AJCC staging system reflects the fact that MMs occur 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. Workup for MM should include clinical examination and CT and/or MRI for paranasal sinus disease and appropriate imaging for other mucosal sites. PET scanning may be considered to define the presence of distant disease in more advanced situations.

Treatment of the Primary

Although limited data exist on treatment options, primary treatment should be surgical for stage III-IVA disease; however, surgery is not recommended for stage IVB-C disease.[225] Adjuvant radiation appears effective in improving local control and survival in most case series.[226] Radiation is clearly indicated in more advanced cases as an adjunct to surgery.[227] The role of radiation in stage III disease is not clear, but it can be considered and should be determined on an individual basis by the treating clinicians. The NCCN strongly encourages clinical trials for all patients with MM to better define treatment choices at all stages of the disease.

Treatment of the Neck

Neck dissection and postoperative radiation are recommended for clinical nodal disease.[228,229] The role of elective neck treatment is unclear. The extension of elective treatment to the neck seems unwarranted in most cases of N0 paranasal sinus MM (see MM-2). However, for oral cavity disease, the likelihood of positive disease is significantly higher and the treatment can be better localized to the ipsilateral neck with both surgery and radiation (see MM-3). Therefore, elective treatment to the neck for oral cavity MM appears justifiable.

Radiation Therapy

Prospective trials evaluating the role of radiotherapy in mucosal melanoma are lacking. However, recently reported results of a randomized trial in cutaneous melanoma are considered relevant to mucosal melanomas in the postoperative setting after neck dissection (see third paragraph in this section).[230] Retrospective studies in mucosal melanoma have shown local recurrence to be common after surgery alone.[231] After using postoperative radiation, lower rates of local and neck recurrence have been seen in historical comparison series.[226,232] Reasonable local control outcomes using radiotherapy alone in unresectable or medically inoperable cases have been reported in small cohort series of mucosal melanomas.[233-235]

Radiotherapy is often recommended in the postoperative management of mucosal melanomas. Primary size or thickness is not used as a risk

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factor when considering radiotherapy 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 MM-2). 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 MM-3).

Indications for postoperative radiation to the neck are generally extrapolated from cutaneous melanoma. Recently, an Australian-New Zealand consortium reported on a randomized trial (250 patients) of postoperative radiotherapy versus observation in patients with palpable adenopathy from cutaneous primaries. Postoperative radiotherapy was associated with a significant reduction in relapse in the nodal basin (19% versus 31%) and a significant improvement in lymph node field control.[230] Only 20 patients relapsed who received RT, whereas 34 patients relapsed who received observation only (P = .04). Considering this trial and retrospective studies in mucosal melanoma, we recommend postoperative radiotherapy for the following high-risk features: extracapsular disease, involvement of 2 or more neck or intraparotid nodes, any node 3 cm or greater, neck excision (alone) with no further basin dissection, or recurrence in the neck or soft tissue after initial surgical resection.[236,237]

Conventional fractionation at 2 Gy per fraction to a total postoperative dose of 60-66 Gy, or to 70 Gy for gross disease, is recommended. While the Australian-New Zealand randomized trial used 48 Gy in 20 fractions (240 cGy/fraction) to neck, axilla, or groin,[230] the 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. IMRT may be very useful in helping to achieve homogenous dose distributions and sparing of critical organs, especially in paranasal sinus sites. There are reports of good outcomes with the use of hypofractionation in cutaneous melanomas which carries the advantage of convenience, but no clear cancer control advantage. There is little experience using large dose per fraction in mucosal sites. Due to the close proximity of neural structures and risk of late effects, hypofractionation (if used) must be carefully planned and delivered.

Systemic Therapy

The role of systemic therapy is discussed in the NCCN [cutaneous] Melanoma Guidelines and should be consulted for management recommendations for systemic disease.

Follow-up

Recommendations are provided in the algorithm (see FOLL-A). Note that physical examination should include endoscopic inspection for paranasal sinus disease.

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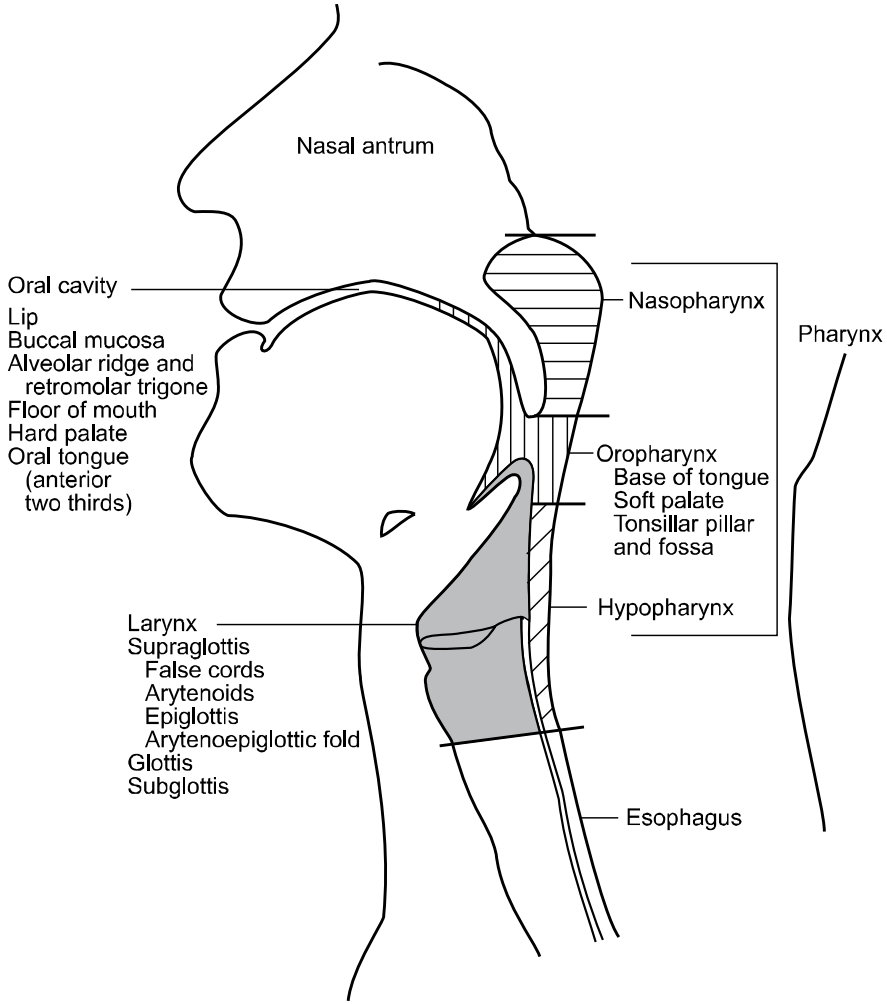
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Figure 1

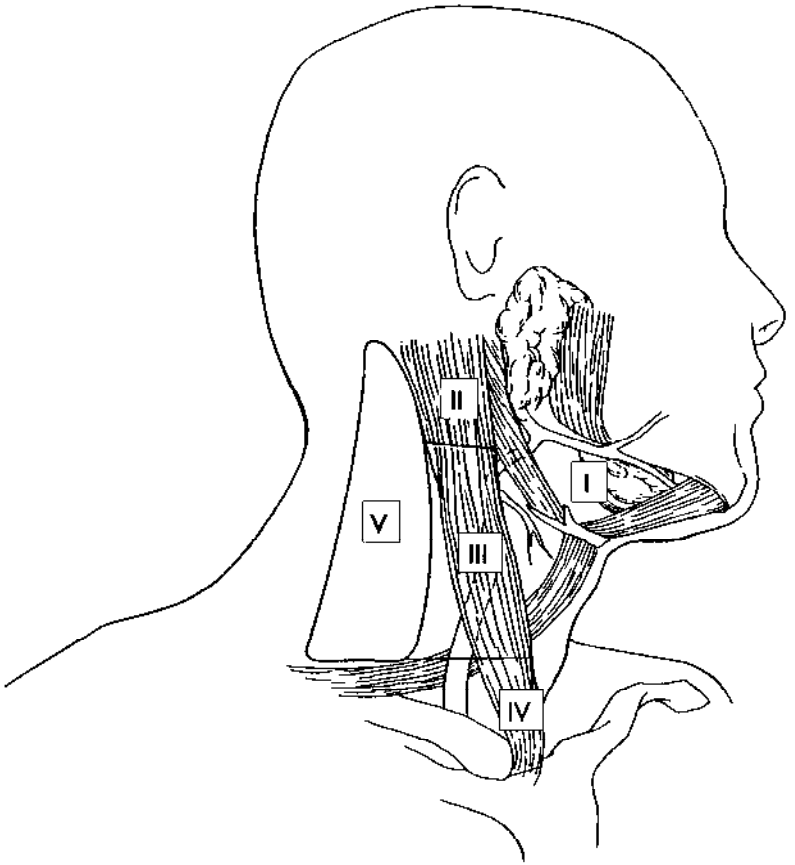
Anatomic sites and subsites of the head and neck



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Figure 2

Level designation for cervical lymphatics in the right neck



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