National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thyroid Carcinoma

Version 2.2014

NCCN.org

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Thyroid Carcinoma

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2014 of the NCCN Guidelines for Thyroid Carcinoma from the 1.2014 Version include:

MS-1

- **The Discussion section was updated to reflect the changes in the algorithm.**

Version 1.2014 of the NCCN Guidelines for Thyroid Carcinoma from the 2.2013 Version include:

Thyroid Carcinoma Nodule Evaluation

THYR-1

- **Workup; After "Radioiodine imaging": "Cold or warm" changed to "*Hypofunctional*".**

THYR-2

- **Footnote "d" is new to the algorithm: "*Ultrasound features associated with low suspicion of malignancy include: isoechoic or hyperechoic solid nodules; mixed solid/cystic nodules without microcalcification, irregular margins, or extrathyroidal extension; or spongiform nodules.*"**
- **Footnote "f" is new: "*Tg washout may be helpful in diagnosis of lymph node metastases*"**

THYR-3

- **Pathway for "Follicular or Hürthle cell neoplasm" was revised extensively.**
- **Pathway for "Follicular lesions of undetermined significance (FLUS)" revised to include recommendations for "*Atypia of undetermined significance (AUS)*".**

THYR-4

- **"This is a new page that includes treatment recommendations for "Follicular or Hürthle cell neoplasm or AUS/FLUS" .**

THYR-A

- **First bullet; First sub-bullet: Sentence revised, "In general, patients with known *structural* residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range".**

THYR-B

- **This is a new page that provides recommendations for the use of oral kinase inhibitors for advanced thyroid cancer.**

Papillary Carcinoma

PAP-1

- **Under Preoperative or Intraoperative Decision-Making Criteria:**
  - **Indications for total thyroidectomy(any present):**
    - ◊ **Bullet added: "*Poorly differentiated*"**
    - ◊ **"Age < 15y or > 45y" and "Aggressive variant" deleted.**
  - **Indications for total thyroidectomy or lobectomy, (if all present):**
    - ◊ **"Age < 15y- 45y" and "No aggressive variant" deleted.**
- **Under Primary Treatment *(also for* (FOLL-1) and (HÜRT-1)*)*:**
  - **Total Thyroidectomy statement deleted: "If lymph nodes palpable or biopsy positive: Central neck dissection (level VI), Lateral neck dissection (levels II, III, IV, and Vb, include levels 1 and Va if clinically involved). Consider preservation of the cervical sensory nerves" and revised: *"Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease."***
  - **Statement amended: ~~If node(s) negative~~, "Consider prophylactic central neck dissection (level VI) (category 2B)"**
  - **For "Lobectomy + isthmusectomy (category 2B)" under "Any of the following:"**
    - ◊ **Second bullet revised: "Positive *resection* margins"**
    - ◊ **Fifth bullet revised: "~~Confirmed~~ *Macroscopic nodal* metastasis"**
- **Footnote "a" was added: "*See ST-1 for staging" (Also for* (FOLL-1) (HÜRT-1) and (MEDU-1)*)***
- **Footnote "d" is new to the algorithm: "*Completion thyroidectomy is not required for small volume pathologic N1 micrometastases (≤ 5 involved nodes, all < 0.2cm in largest dimension).*"**

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Papillary Carcinoma continued

PAP-1 continued

- Footnote deleted: "For microcarcinoma (< 1cm), a total thyroidectomy may not be needed. Age is an approximation and not an absolute determination."
- Footnote deleted: "Tall cell variant, columnar cell, or poorly differentiated features."

PAP-2

- For "Clinical Presentation": "Papillary carcinoma found post-lobectomy"
  - Under "Any of the following":
    - ◊ Bullet two revised: "Positive *resection* margins"
    - ◊ Bullet eight added: *"Poorly differentiated"*
- Third column; Middle pathway: "Lymphovascular invasion" was added to list of features.
- Under "All of the following":
  - Bullet one revised: "Negative *resection* margins"
- Footnote deleted: "Tall cell variant, columnar cell, or poorly differentiated features."

PAP-3 (Also for (FOLL-2) and (HÜRT-2))

- Gross residual disease in neck; Unresectable pathway:
  - Bullet one: "TSH + Tg measurement + antithyroglobulin antibodies (~~2~~ *6*-12) wks postoperatively"

PAP-4

- The recommendations on this page were extensively revised including: (Also for (FOLL-3) and (HÜRT-3))
  - Revisons were made to the list of "Clinicopathologic Factors" for each pathway.
  - Second column; title changed from "Decision Making for Initial Adjuvant or Therapeutic Adminstration of RAI" to Consideration for Initial Postoperative RAI Therapy".
- *"Consideration For Initial Postoperative RAI Therapy"* is a new page to the guideline. (Also for (FOLL-3) and (HÜRT-3))
- *Footnote "j" revised: (ie, poorly differentiated thyroid carcinoma)*

PAP-5

- Postsurgical Therapy For Patients Being Considered for RAI Therapy page deleted. (Also for (FOLL-4) and (HÜRT-4))

Papillary Carcinoma continued

PAP-5 continued

- *"RAI not Typically Indicated Based on Clinicopathologic Features"* is a new page to the guideline. (Also for (FOLL-4) and (HÜRT-4))

PAP-6 (Also for (FOLL-5) and (HÜRT-5))

- *"RAI Being Considered Based on Clinicopathologic Features"* is a new page to the guideline.

PAP-7 (Also for (FOLL-6) and (HÜRT-6))

- *"Known or Suspected Distant Metastatic Disease"* is a new page to the guideline.

PAP-9 (Also for (FOLL-8) and (HÜRT-8))

- *"Treatment of Metastatic Disease Not Amenable to RAI Therapy"* page extensively revised.
- Footnote "aa" was revised to include axitinib and vandetanib as category 2A, pazopanib changed from category 2B to category 2A, and sorafenib was removed from the footnote and placed in the algorithm. The footnote now reads as follows: "While not FDA approved for treatment of differentiated thyroid cancer, commercially available small molecule kinase inhibitors (such as *axitinib, pazopanib*, sunitinib, or *vandetanib [all are category 2A])* can be considered if clinical trials are not available or appropriate."

Follicular Carcinoma

FOLL-1 (Also for (HÜRT-1) and (FOLL-1))

- Under Primary treatment column:
  - Bullet deleted: "Ultrasound detected or clinically apparent disease."

FOLL-4

- "Postsurgical Therapy For Patients Being Considered For RAI Therapy" page deleted.

FOLL-6

- "Known or Suspected Distant Metastatic Disease" page extensively revised.

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Hürthle Cell Carcinoma

HÜRT-1

- Under "Primary treatment" column:
  Footnote deleted: "Possible benefit to reduce recurrence must be balanced with risk of hypoparathyroidism."

HÜRT-2

- "Unresectable" pathway; Recommendation revised, "No ~~scan~~ *imaging* performed"
- Footnote deleted: Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.+

HÜRT-6

- "Known or Suspected Distant Metastatic Disease" page extensively revised.

Medullary Carcinoma

MEDU-1

- Column heading, "Additional Workup" revised to: *"Diagnostic Procedures"*
- Footnote "a" new to algorithm: "See ST-1 for staging."
- Footnote "c" revised to: "Evidence of pheochromocytoma should be evaluated and ~~treated~~ *addressed* appropriately before proceeding to the next step on the pathway."

MEDU-5

- "Basal calcitonin undetectable or CEA within reference range"; Observe pathway: Bullet five revised to: "For MEN 2B or 2A, annual *biochemical* screenings for pheochromocytoma and hyperparathyroidism (MEN 2A)"
- Under fifth column:
  - "Positive" revised to: *"Positive result"*
  - "Negative" revised to: *"Negative result"*
- Footnote "l" added*:*
  "(See page (PHEO-1) from NCCN Guidelines for Neuroendocrine Tumors)"

Medullary Carcinoma continued

MEDU-6

- Recurrent or Persistent Disease amended to include: *"Locoregional disease"*
- For Locoregional disease the following recommendations were revised:
  - "Surgical resection ~~± postoperative EBRT~~ is *the preferred treatment modality"*
  - "~~Consider~~ EBRT *can be considered for unresectable disease or, less commonly, after surgical resection*"
  - *"Observe"* added as treatment option
- Footnote "o" new to algorithm: *"Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. "See Principles of Kinase Inhibitor Therapy (THYR-B)."*

MEDU-7

- The recommendations on this page were extensively revised including:
  - *Title changed to"Recurrent or Persistent Disease Distant Metastases"*
  - First column: Previously there were three pathways for "Locoregional," Symptomatic, distant metastases," and Asymptomatic, distant metastases". There are now two pathways: "Asymptomatic disease" and "Symptomatic disease or progression"
  - Footnote "p" new to algorithm: *"Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease*". See Principles of Kinase Inhibitor Therapy for Advanced Thyroid Cancer (THYR-B).
  - Footnote "q" new to algorithm: "*Clinical benefit can be seen in both sporadic and familial MTC."*
  - Footnote "s" revised to: "Denosumab and *bisphosphonates* can be associated with severe hypocalcemia: patients with hypoparathyroidism and vitamin D deficiency are at increased risk."

Anaplastic Carcinoma

ANAP-1

- **The algorithm for the treatment of Anaplastic Carcinoma was extensively revised including:**
  - **Diagnostic Procedures:**
    - ◊ **"CBC *with differential*"**
    - ◊ ***"Comprehensive chemistry (calicum, phosphorus)"***
    - ◊ ***"Neck ultrasound"***
    - ◊ **"*CT* head, neck, chest, abdomen, pelvis"**
    - ◊ ***"Fiberoptic (or mirror laryngoscopy)"***
    - ◊ ***"In case of airway invasion, bronchoscopy"***
    - ◊ **"Consider ^{18}FDG-PET ± /CT ~~scan"~~**
  - **"Establish Goals of Therapy" is a new section for the page**
  - **Treatment recommendations for anaplastic thyroid carcinoma were added based on stage of disease**

ANAP-2

- **This is a new page that includes recommendations for the treatment of "Metastatic disease" and recommendations for "Surveillance and Management"**

ST- 1 Staging

"Table 1: American Joint Committee on Cancer (AJCC): TNM Staging for Thyroid Cancer" revised to include:

"Residual Tumor (R)
Classification of relevance to assess impact
of surgery on outcomes:
R0 No residual tumor
R1 microscopic residual tumor
R2 macroscopic residual tumor
Rx presence of residual tumor cannot be determined"

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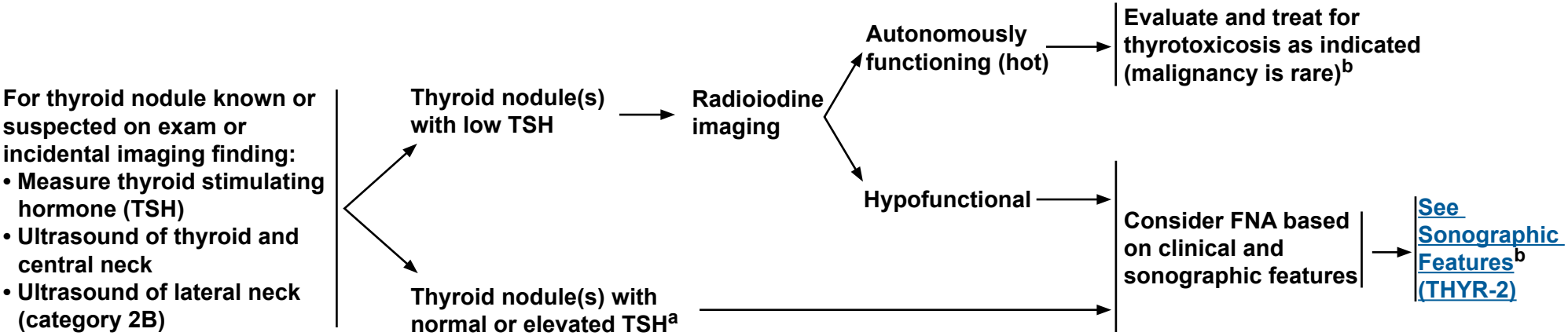
CLINICAL PRESENTATION **WORKUP**



[a]Evaluate and treat for hypothyroidism as clinically indicated.
[b]For nodules not meeting criteria for FNA, or nodules that appear to be benign by scan or FNA, surveillance should include repeat ultrasound after 6-12 months; if stable for 1-2 years, then subsequent ultrasound can be considered at 3-5 year intervals.

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SONOGRAPHIC FEATURES	Threshold for FNA
Solid nodule	
• With suspicious sonographic features[c]	≥ 1.0 cm
• Without suspicious sonographic features[d]	≥ 1.5 cm
Mixed cystic-solid nodule	
• With suspicious sonographic features[c]	≥ 1.5-2.0 cm
• Without suspicious sonographic features[d]	≥ 2.0 cm
Spongiform nodule[e]	≥ 2.0 cm
Simple cyst	Not indicated[g]
Suspicious cervical lymph node[f]	FNA node ± FNA associated thyroid nodule(s)

→ **FNA, if indicated**
(See THYR-3 and THYR-4)
or
Observe[b]

The above criteria serve as general guidelines. In patients with high-risk clinical features,[h] evaluations of nodules smaller than listed may be appropriate depending upon clinical concern. Allowance for informed patient desires would include excisional biopsy (lobectomy or thyroidectomy) for definitive histology, especially in larger nodules (>4 cm) or higher risk clinical situations.

[b]For nodules not meeting criteria for FNA, or nodules that appear to be benign by scan or FNA, surveillance should include repeat ultrasound after 6-12 months; if stable for 1-2 years, then subsequent ultrasound can be considered at 3-5 year intervals.
[c]Suspicious sonographic features: Hypoechoic, microcalcifications, increased central vascularity, infiltrative margins, taller than wide in transverse plane.
[d]Ultrasound features associated with low suspicion of malignancy include: isoechoic or hyperechoic solid nodules; mixed solid/cystic nodules without microcalcification, irregular margins, or extrathyroidal extension; or spongiform nodules.
[e]Aggregation of multiple microcystic components in more than 50% of the volume of the nodule.
[f]Tg washout may be helpful in diagnosis of lymph node metastases.
[g]Except as therapeutic modality.
[h]High-risk clinical features: radiation exposure as child or adolescent; first degree relative with thyroid cancer or MEN2; FDG avid on PET scan; personal history of thyroid cancer-associated conditions such as familial adenomatous polyposis, Carney complex, Cowden syndrome; personal history of thyroid cancer in lobectomy.

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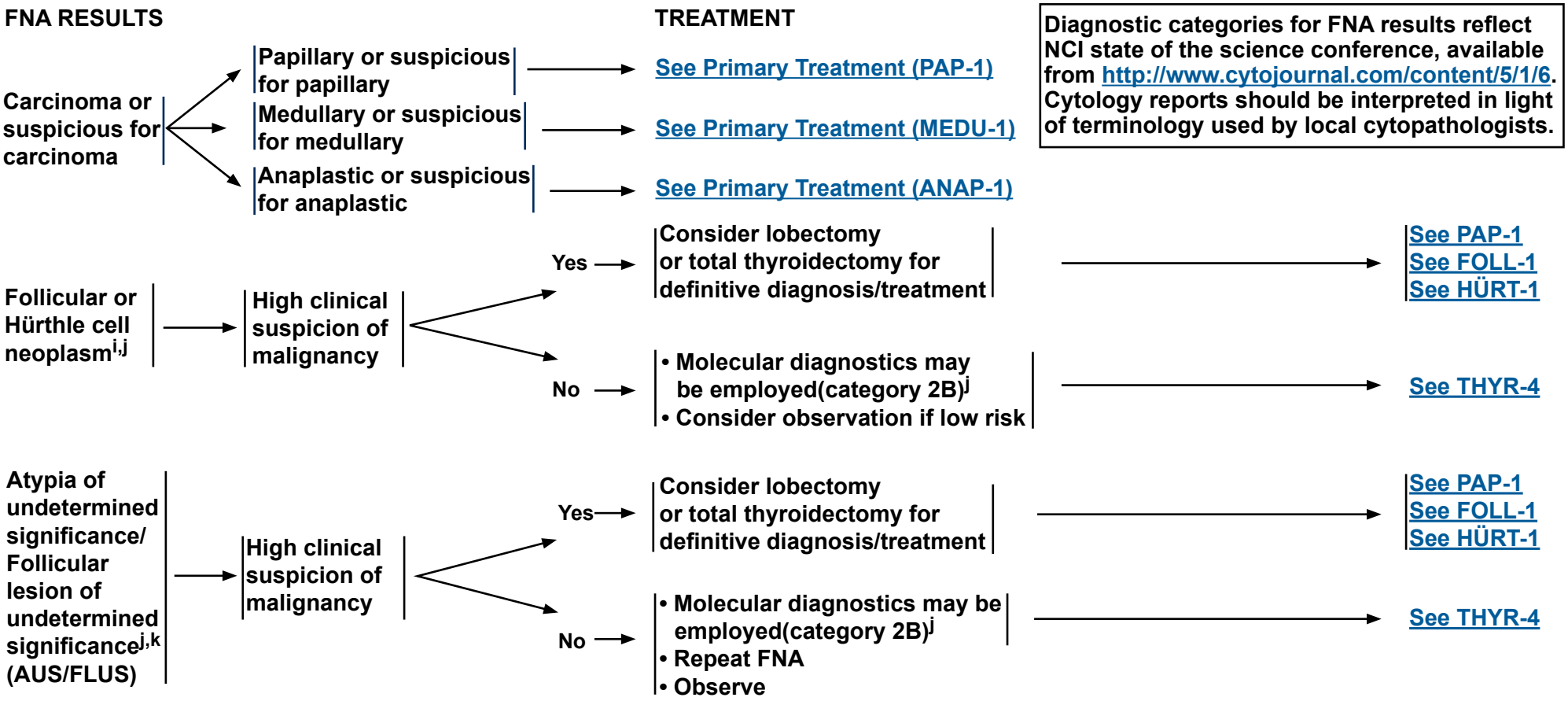

[i]Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 20%-30%.

[j]The diagnosis of follicular carcinoma or Hurtle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, Hürthle cell neoplasm, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (FLUS)) as they are more likely to be benign or more likely to be malignant. If molecular testing suggests papillary thyroid carcinoma, see (PAP-1). If molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less),consider observation.

[k]Alternative terms include: rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%-10%.

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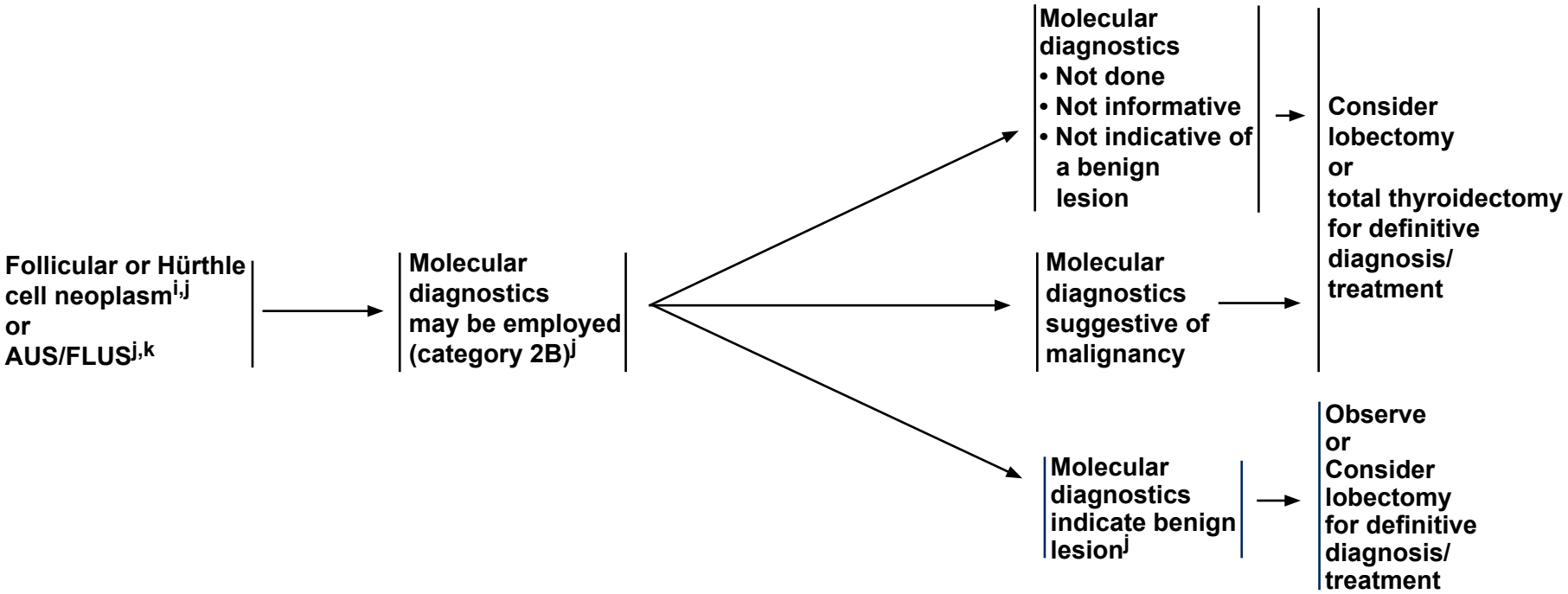
FNA RESULTS **TREATMENT**



[i]Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 20%-30%.

[j]The diagnosis of follicular carcinoma or Hurtle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, Hürthle cell neoplasm, atypia of undetermined significance(AUS), follicular lesions of undetermined significance (FLUS) as they are more likely to be benign or more likely to be malignant. If molecular testing suggests papillary thyroid carcinoma, see (PAP-1). If molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation.

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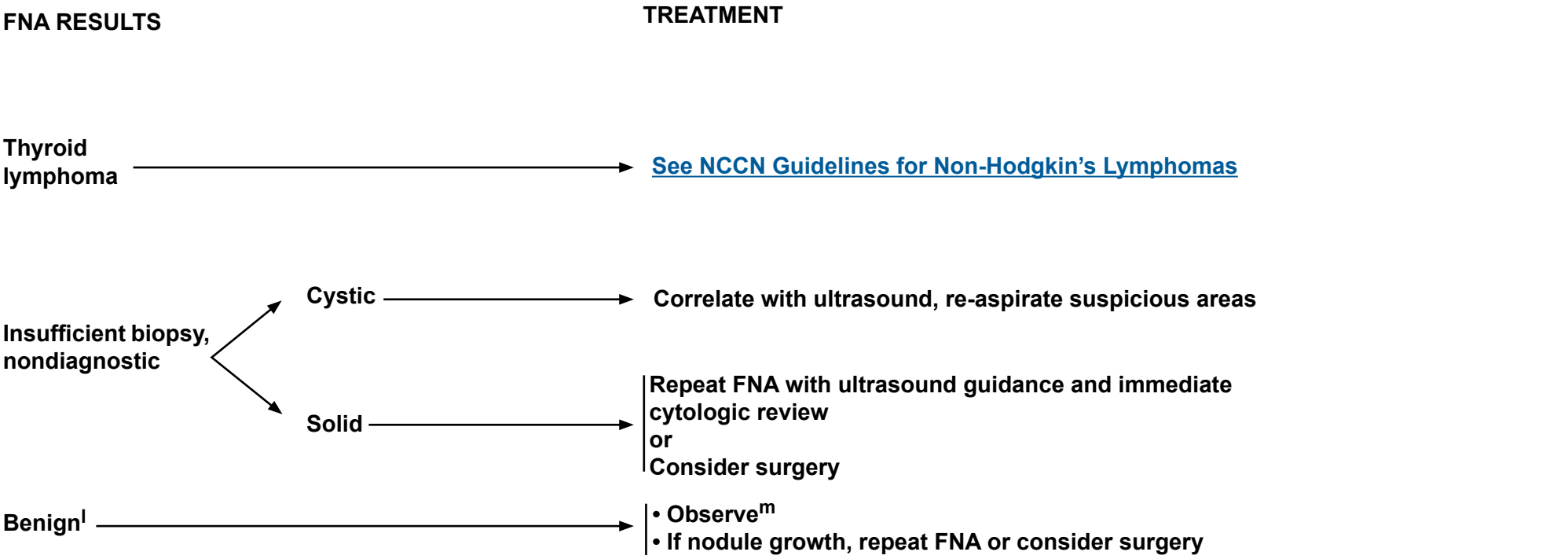

[l]Includes nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, and Hashimoto's thyroiditis. Estimated risk of malignancy is approximately 5% or less; consider observation.

[m]Repeat ultrasound after 6-12 mo, if stable for 1-2 years, then subsequent ultrasound can be considered at 3-5 year intervals.

Diagnostic categories for FNA results reflect NCI state of the science conference, available from http://www.cytojournal.com/content/5/1/6. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

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PRINCIPLES OF THYROID STIMULATING HORMONE (TSH) SUPPRESSION

- **Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH.**
  - **In general, patients with known structural residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range.**
  - **For low-risk patients with biochemical evidence but no structural evidence of disease (eg, Tg positive, but imaging negative), maintain TSH levels at 0.1 - 0.5 mU/L.**
  - **Patients who remain disease free for several years can probably have their TSH levels maintained within the reference range.**
- **Given the potential toxicities associated with TSH-suppressive doses of levothyroxine---including cardiac tachyarrhythmias (especially in the elderly) and bone demineralization (particularly in post-menopausal women) as well as frank symptoms of thyrotoxicosis---the risk and benefit of TSH-suppressive therapy must be balanced for each individual patient.**
- **Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/day) and vitamin D (1000 units/day).**

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PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CANCER

- **Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo controlled clinical trials in locally recurrent unresectable and metastatic medullary thyroid cancer (MTC) and in radio-iodine refractory differentiated thyroid cancer (DTC).[1,2,3]**
- **When considering kinase inhibitor therapy for individual patients, several factors should be considered.**
  - **Kinase inhibitor therapy can be associated with progression free survival, but is not curative.**
  - **Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.**
  - **The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.**
- **The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have side effects.**
- **Optimal management of kinase inhibitor side effects is essential. Where available, guidelines outlining the management of the dermatologic, hypertensive and gastrointestinal side effects of kinase inhibitors can be used.[4,5,6] In addition, dose modification can be considered, including dose holds and dose reductions.**

[1]Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134-141.
[2]Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. Lancet 2014;384(9940):319-328.
[3]Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639-3646.
[4]Burtness B, Anadkat M, Basti S, et al. NCCN Task Force Report: Management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer. J Natl Compr Canc Netw 2009;7 Suppl 1:S5-S21.
[5]Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician's perspective. Semin Oncol 2014;41 Suppl 2:S1-S16.
[6]Carhill AA, Cabanillas ME, Jimenez C, et al. The noninvestigational use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. J Clin Endocrinol Metab 2013;98:31-42.

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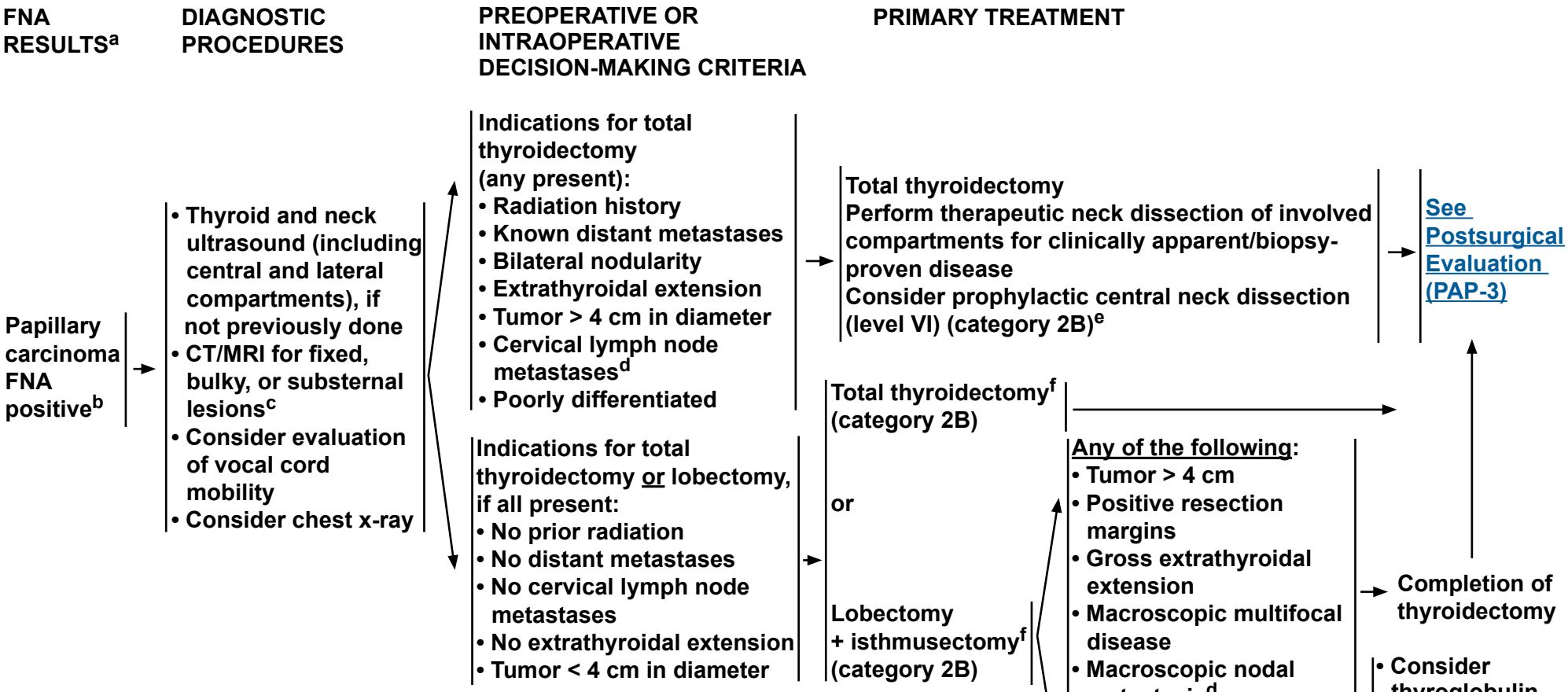

[a] See ST-1 for staging.
[b] There is a potential role for lobectomy with or without frozen section if FNA is suspicious but not diagnostic for papillary carcinoma.
[c] Use of iodinated contrast will delay treatment with RAI but is required for optimal cervical imaging using CT.
[d] Completion thyroidectomy is not required for small volume pathologic N1 micrometastases (≤ 5 involved nodes, all < 0.2cm in largest dimension).
[e] Possible benefit to reduce recurrence must be balanced with risk of hypoparathyroidism.
[f] The majority of the panel would recommend total thyroidectomy for biopsy proven papillary thyroid carcinoma.
[g] See Principles of TSH Suppression (THYR-A).

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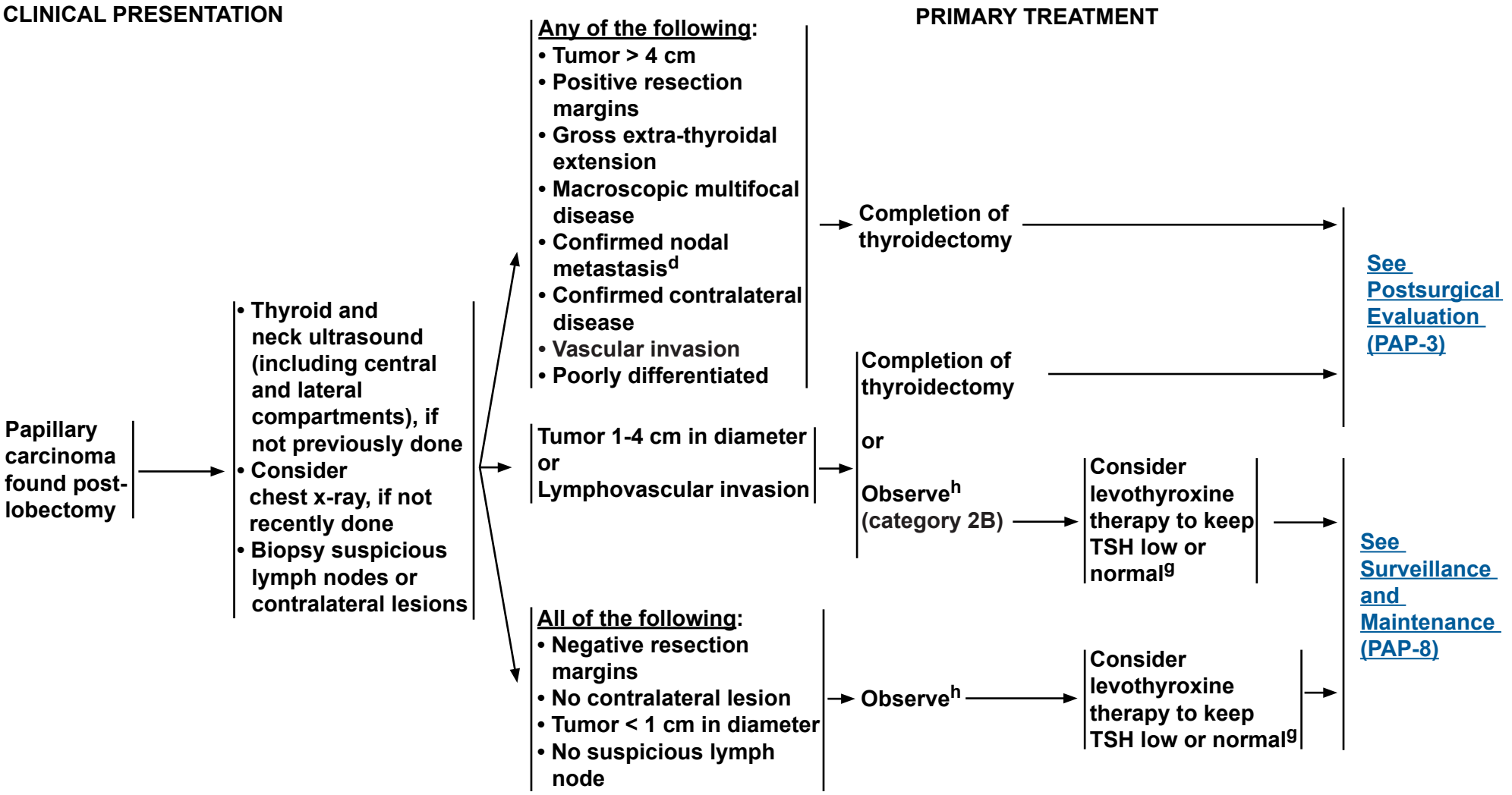

[d]Completion thyroidectomy is not required for small volume pathologic N1 micrometastases (≤ 5 involved nodes,all < 0.2cm in largest dimension).
[g]See Principles of TSH Suppression (THYR-A).
[h]Measurement of thyroglobulin and antithyroglobulin antibodies.

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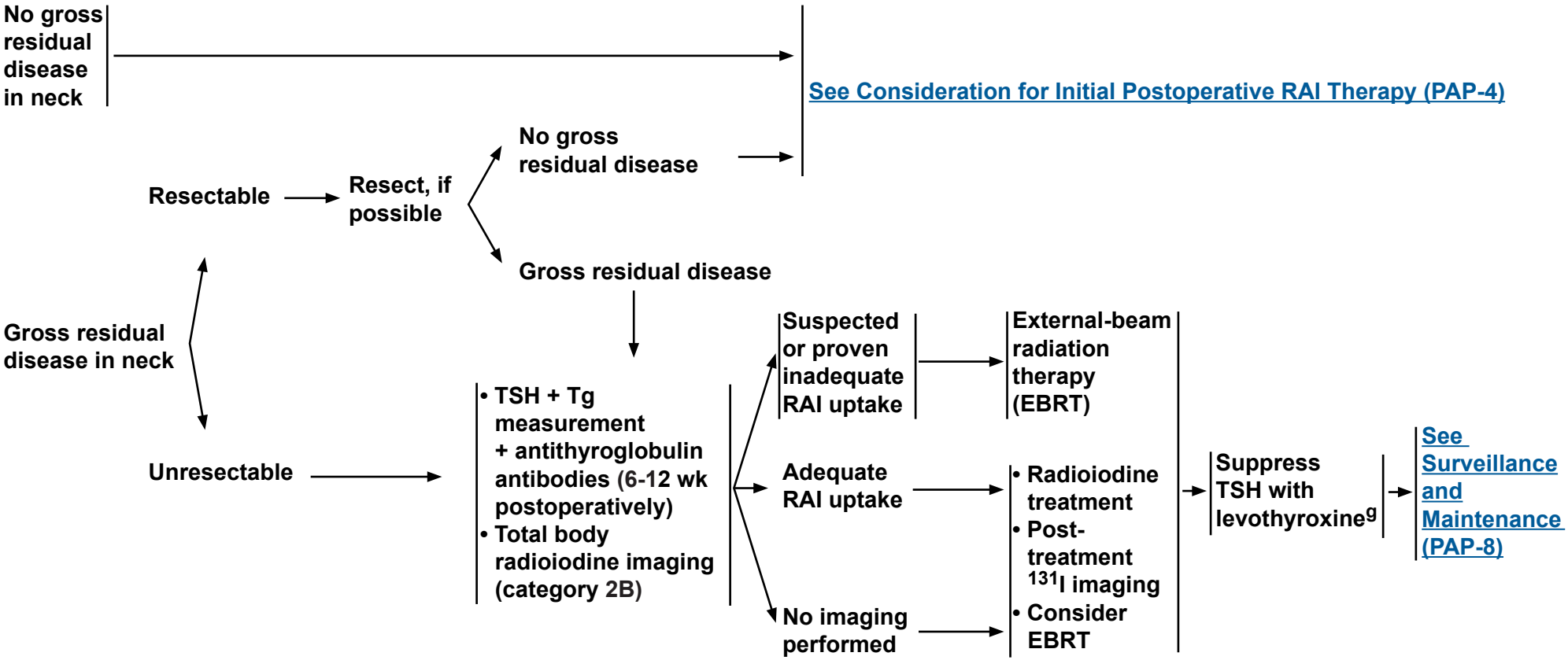
POSTSURGICAL EVALUATION



[g] See Principles of TSH Suppression (THYR-A).

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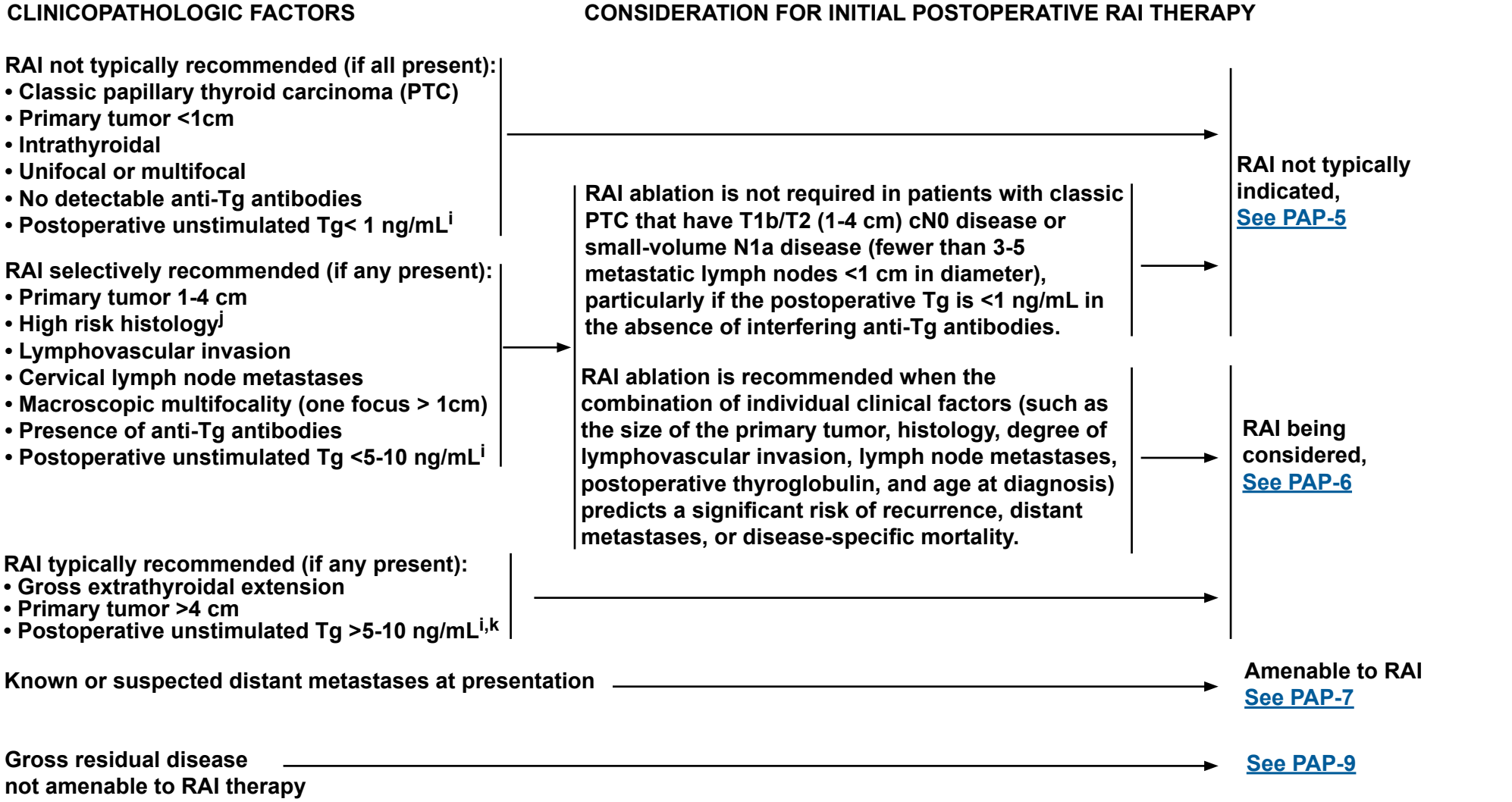
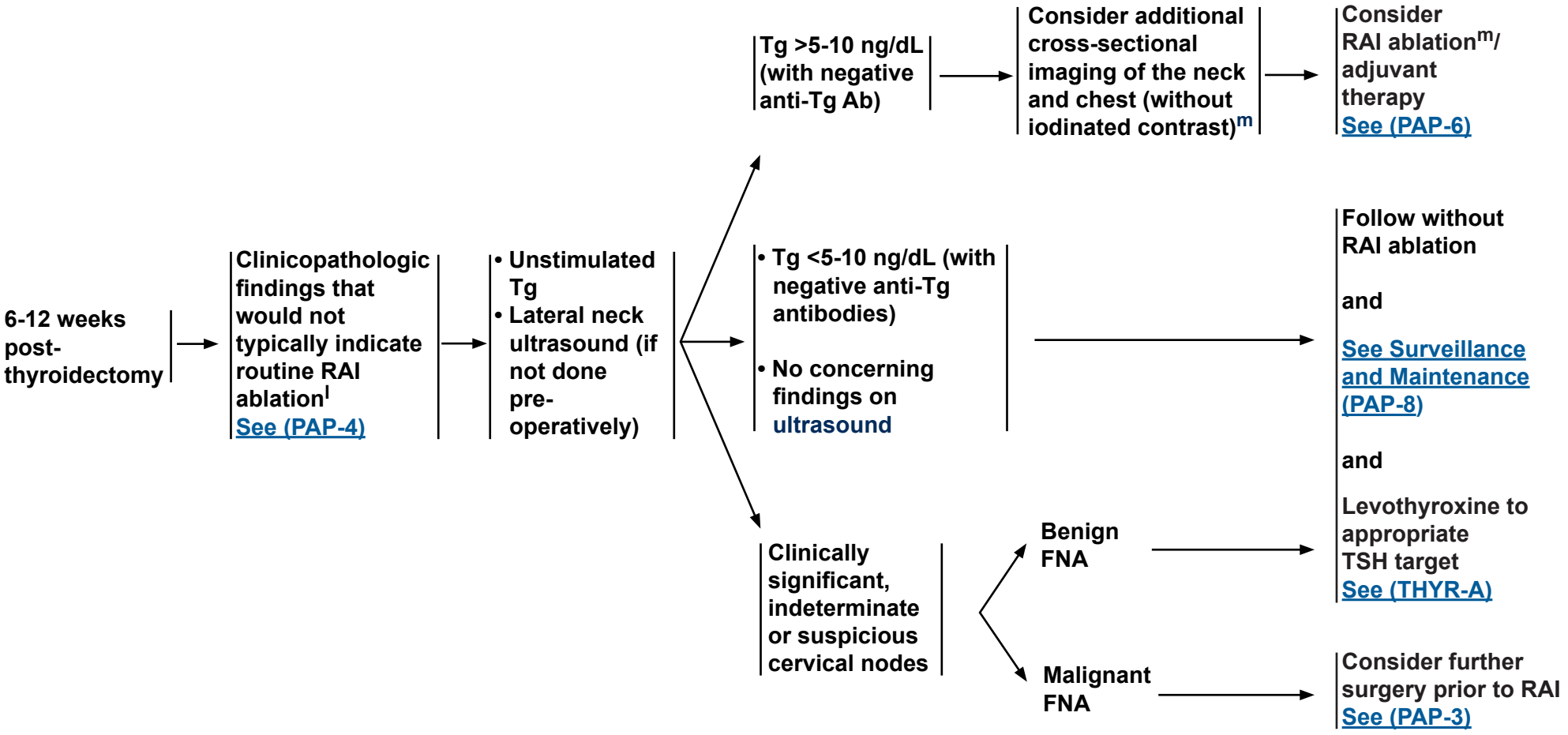


[i]Tg values obtained 6-12 weeks after total thyroidectomy.
[j](ie, poorly differentiated thyroid carcinoma).
[k]Additional cross sectional imaging should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

For general principles related to radioactive iodine therapy, See (Discussion)

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

RAI NOT TYPICALLY INDICATED BASED ON CLINICOPATHOLOGIC FEATURES



[l]For example, RAI ablation is not required in patients with classic PTC that have T1b/T2 (1-4 cm) cN0 disease or small-volume N1a disease (fewer than 3 metastatic lymph nodes <1 cm in diameter), particularly if the postoperative Tg is <1 ng/mL in the absence of interfering anti-Tg antibodies.
[m]If structural disease is identified, additional evaluation and/or treatment may be clinically indicated.

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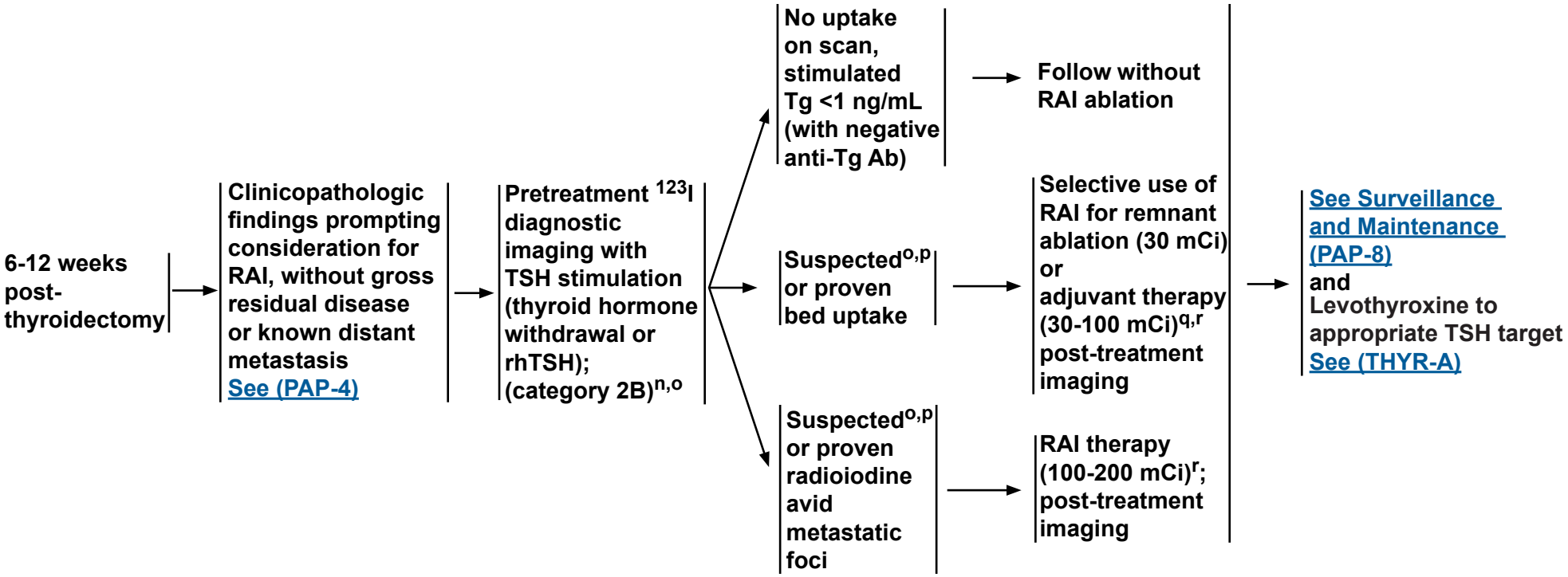
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



[n]Alternatively, low-dose ^{131}I (1-3 mCi) may be used.

[o]While pre-ablation diagnostic scans in this setting are commonly done at NCCN member institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, post-operative Tg, intra-operative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.

[p]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

[q]The administered activity of RAI therapy should be adjusted for pediatric patients.

[r]If RAI ablation is used in T1b/T2 (1-4 cm), clinical N0 disease, 30 mCi of ^{131}I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This RAI ablation dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1-4 cm) with small-volume N1a disease (fewer than 3-5 metastatic lymph node metastases <1 cm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

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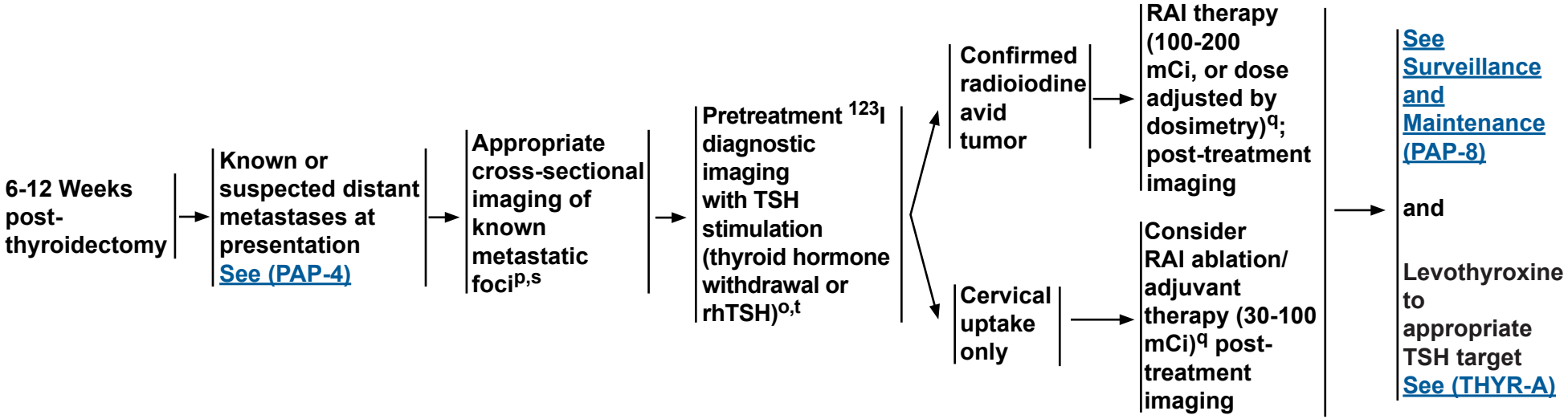
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[o]While pre-ablation diagnostic scans in this setting are commonly done at NCCN member institutions, the panel recommends (category 2B) selective use of pre- ablation diagnostic scans based on pathology, post-operative Tg, intra-operative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.

[p]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

[q]The administered activity of RAI therapy should be adjusted for pediatric patients.

[s]To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection, external beam irradiation) to prevent invasion/compression of vital structures or pathological fracture either as a result of disease progression or TSH stimulation.

[t]If ^{123}I is not available, low-dose ^{131}I (1-3 mCi) may be used. Alternatively, low-dose ^{131}I (1-3 mCi) may be used. Dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound[u]
- Consider TSH stimulated Tg measurement in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[v]
- Consider TSH-stimulated radioiodine imaging in high-risk patients, patients with previous RAI avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance
- In iodine responsive tumors, if detectable Tg or distant metastases or soft tissue invasion on initial staging, radioiodine imaging every 12-24 mo until no clinically significant response is seen to RAI treatment (either withdrawal of thyroid hormone or rhTSH)[w]
- If ^{131}I imaging negative and stimulated Tg > 2-5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT, chest CT, FDG-PET/CT)
- Patients treated with ^{131}I ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulated thyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

RECURRENT DISEASE

- Stimulated Tg 1-10 ng/mL
- Non-resectable tumors
- Non-radioiodine responsive

→ Suppress TSH with levothyroxine[g]

Locoregional recurrence →
Surgery (preferred) if resectable[x] and/or
Radioiodine treatment,[q] if radioiodine imaging positive and/or
EBRT, if radioiodine imaging negative

- Stimulated Tg > 10 ng/mL and rising
- Scans (including PET) negative

→ Consider radioiodine therapy with 100-150 mCi[q] and post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

Metastatic disease → See Treatment of Metastatic Disease (PAP-9)

[g] See Principles of TSH Suppression (THYR-A).
[q] The administered activity of RAI therapy should be adjusted for pediatric patients.
[u] A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[v] In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging. With a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).
[w] If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.
[x] Preoperative vocal cord assessment, if central neck recurrence.

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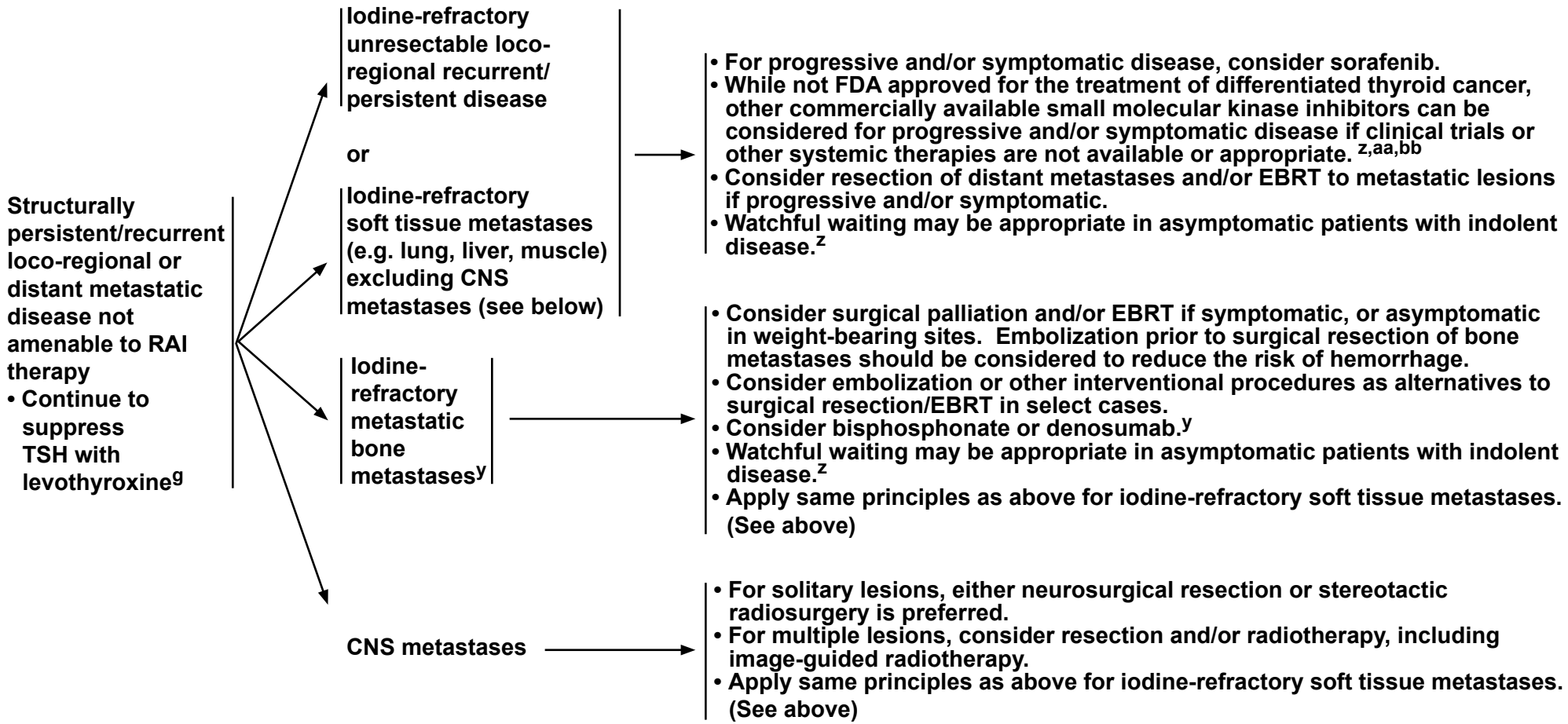
TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



[g] See Principles of TSH Suppression (THYR-A).
[y] Denosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[z] Kinase inhibitor therapy may not be approriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B)
[aa] While not FDA approved for treatment of differentiated thyroid cancer, commercially available small molecule kinase inhibitors (such as axitinib, pazopanib, sunitinib, or vandetanib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[bb] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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NCCN Guidelines Version 2.2014
Thyroid Carcinoma – Follicular Carcinoma

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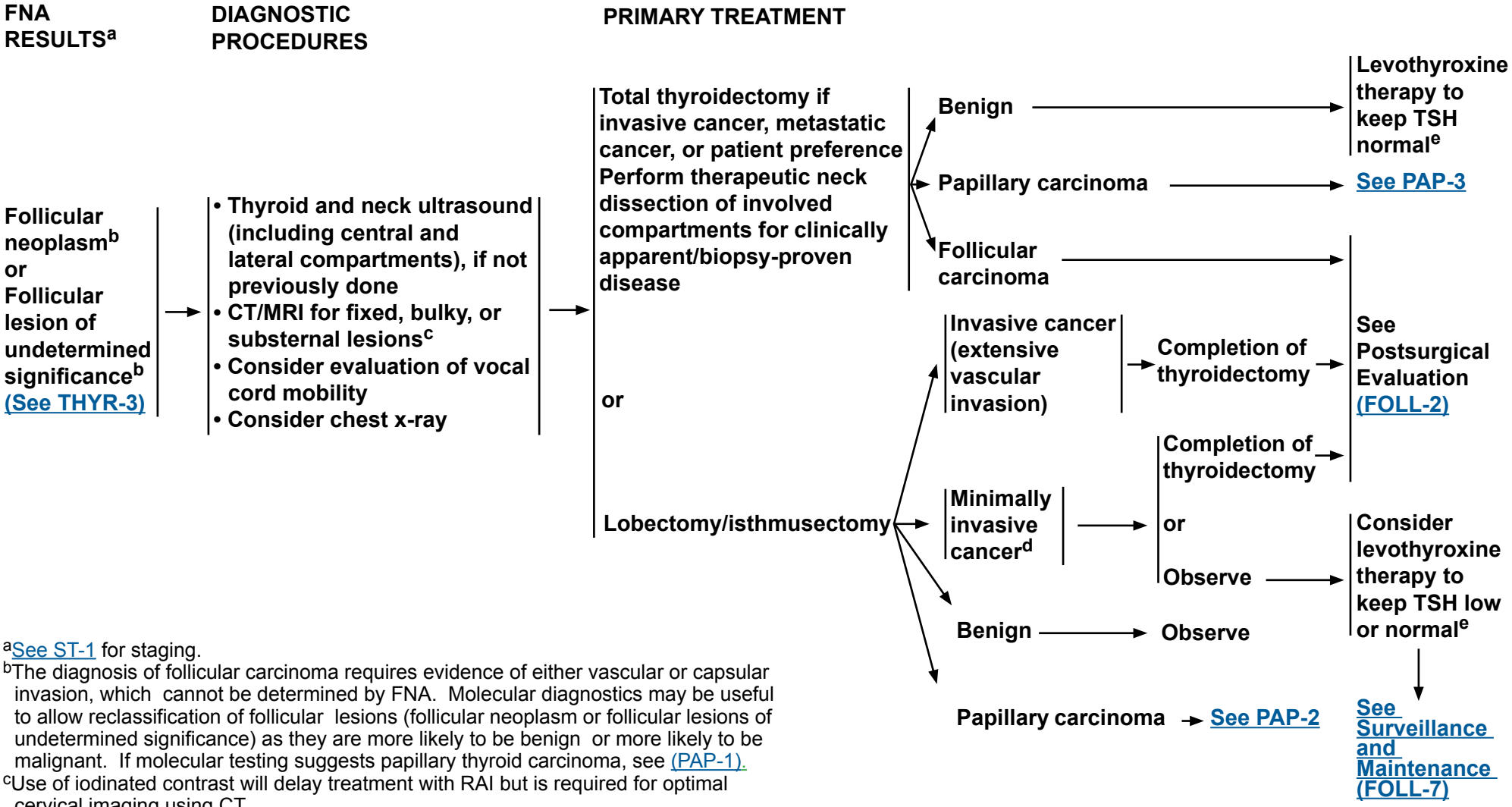

[a] See ST-1 for staging.

[b] The diagnosis of follicular carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (follicular neoplasm or follicular lesions of undetermined significance) as they are more likely to be benign or more likely to be malignant. If molecular testing suggests papillary thyroid carcinoma, see (PAP-1).

[c] Use of iodinated contrast will delay treatment with RAI but is required for optimal cervical imaging using CT.

[d] Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.

[e] See Principles of TSH Suppression (THYR-A).

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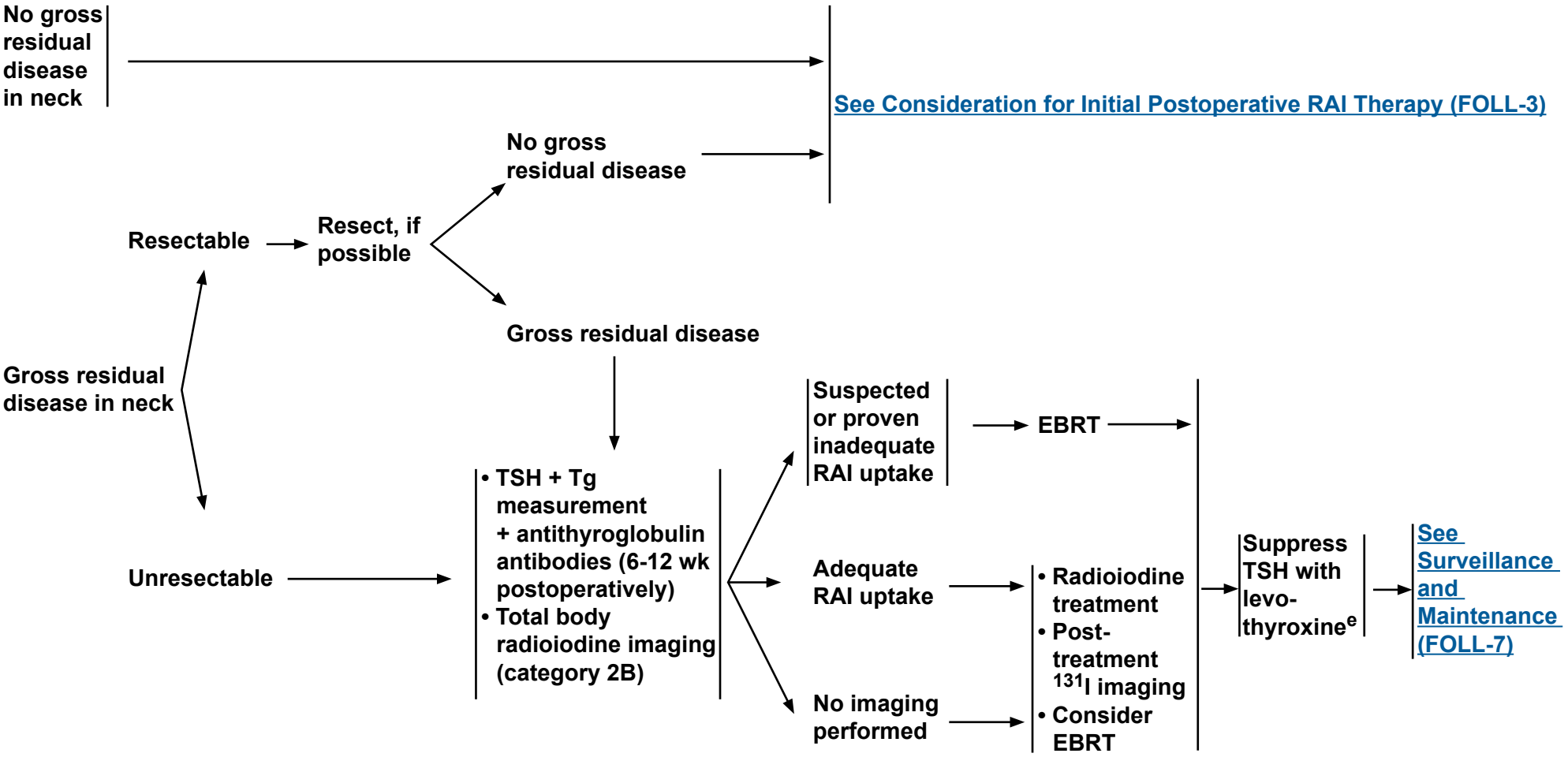
POSTSURGICAL EVALUATION



[e]See Principles of TSH Suppression (THYR-A).

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Thyroid Carcinoma – Follicular Carcinoma

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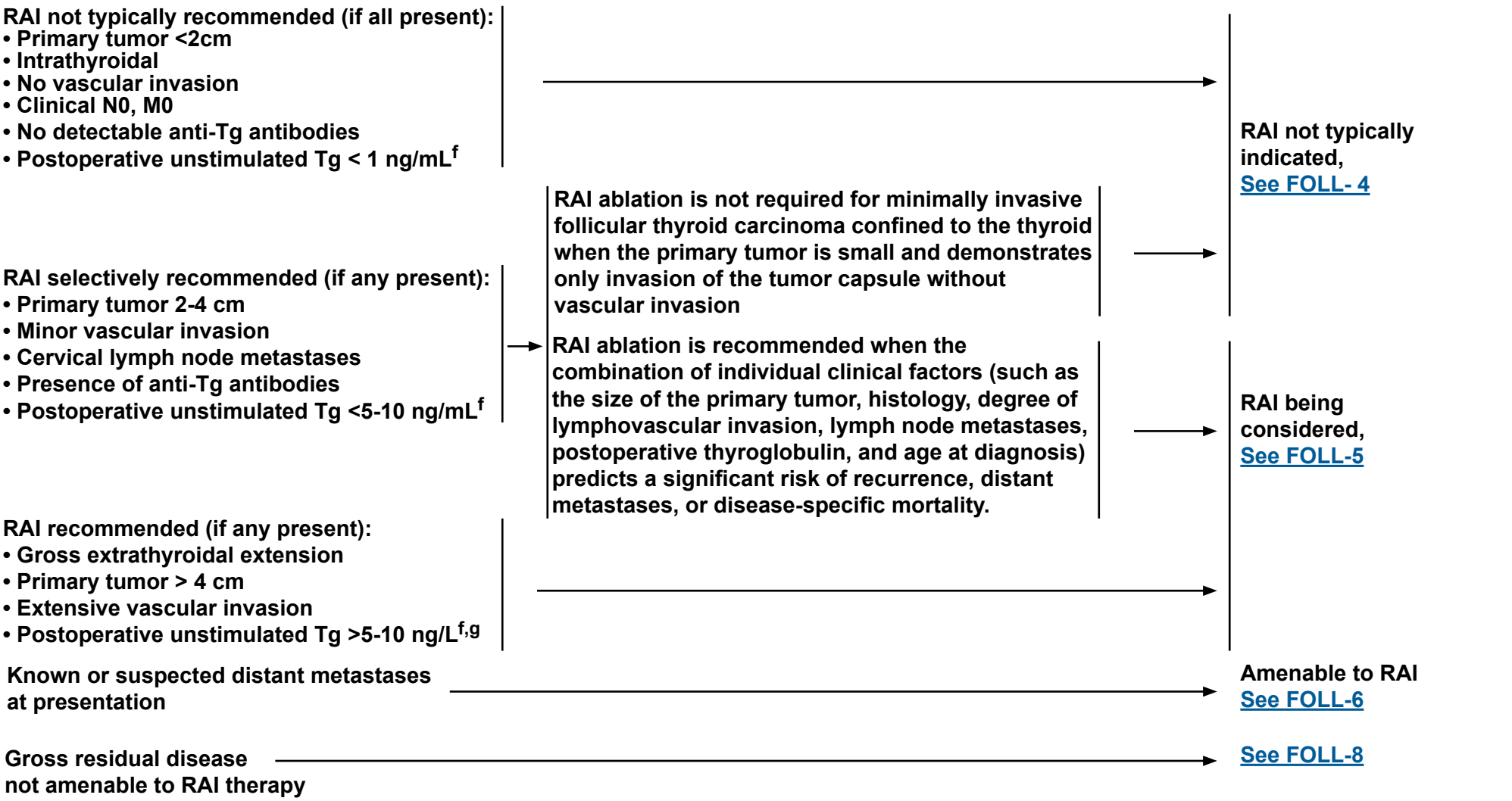

[f]Tg values obtained 6-12 weeks after total thyroidectomy.
[g]Additional cross sectional imaging should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

For general principles related to RAI therapy, See (Discussion)

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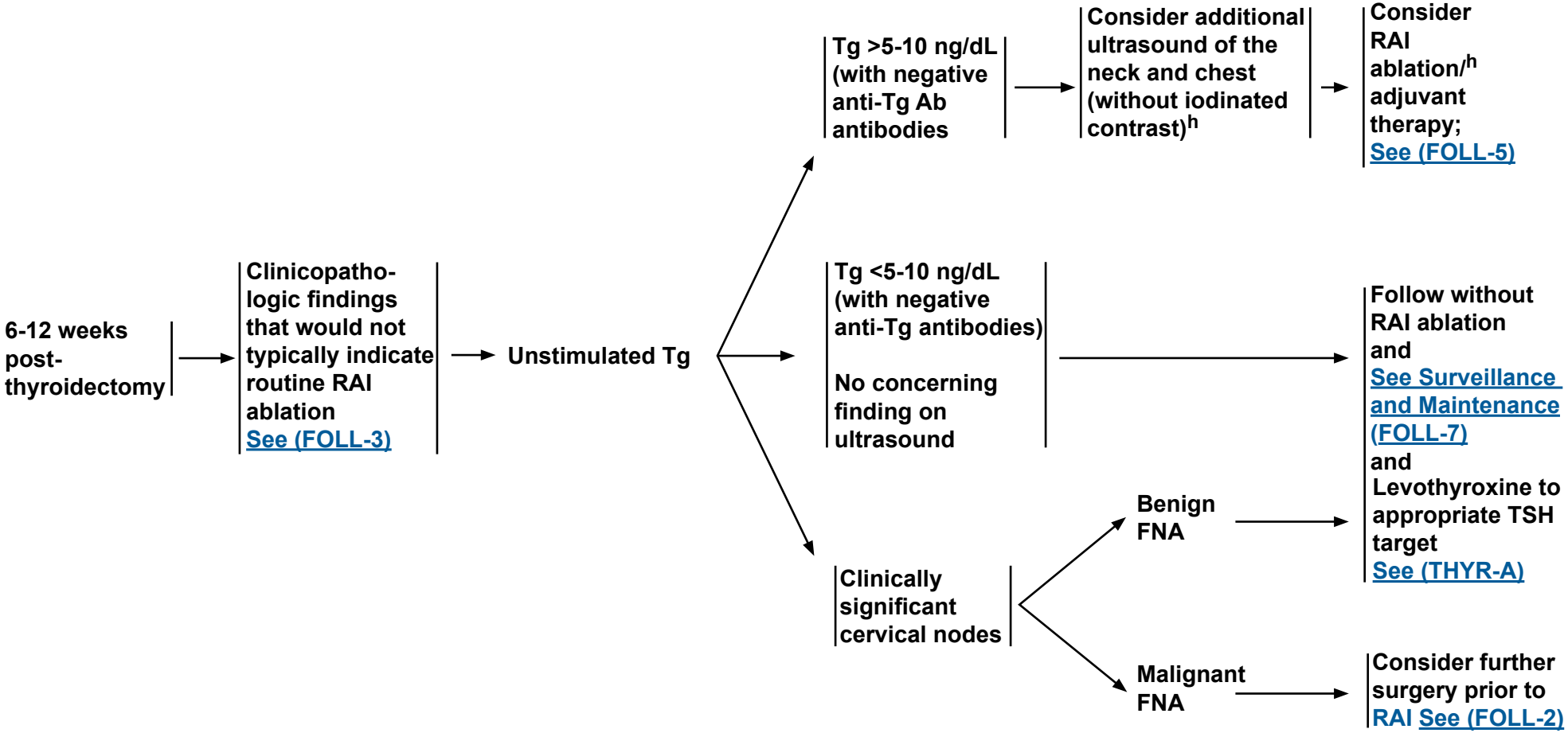

[h]If structural disease is identified, additional evaluation and/or treatment may be clinically indicated.

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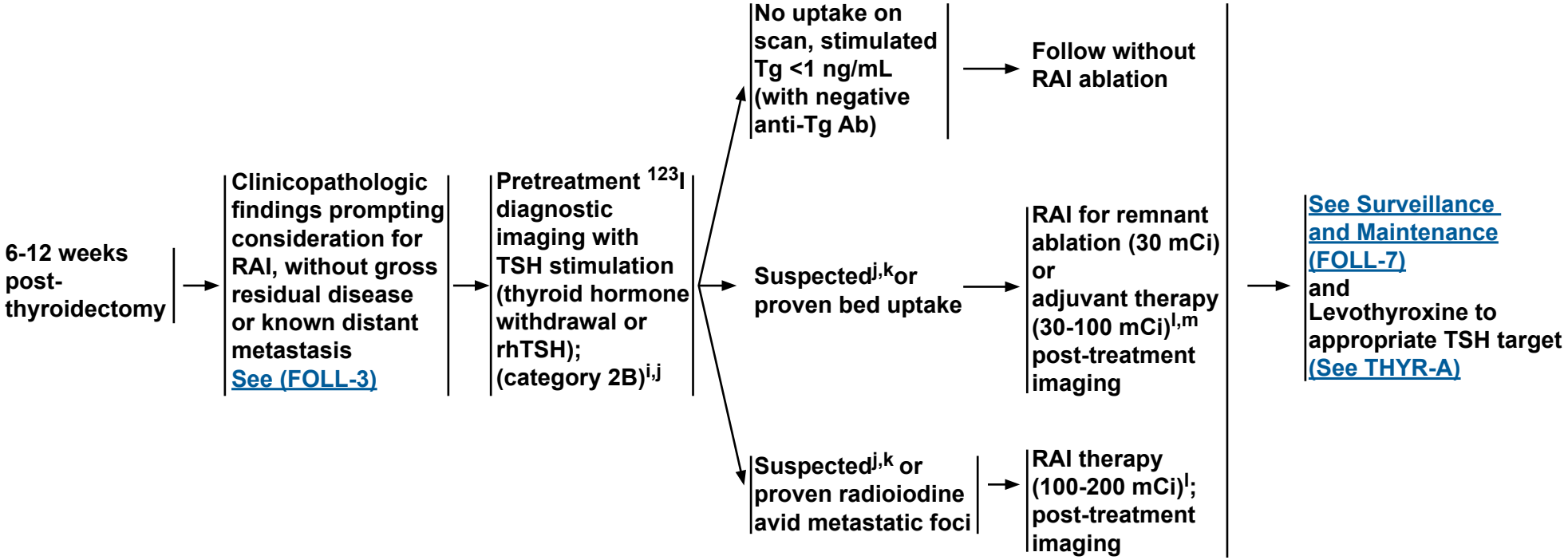
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



[i]Alternatively, low-dose ^{131}I (1-3 mCi) may be used.
[j]While pre-ablation diagnostic scans in this setting are commonly done at NCCN member institutions the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, post-operative Tg, intra-operative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.
[k]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.
[l]The administered activity of RAI therapy should be adjusted for pediatric patients.
[m]If RAI ablation is used in T1b/T2 (1-4 cm), clinical N0 disease, 30 mCi of ^{131}I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This RAI ablation dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1-4 cm) with small-volume N1a disease (fewer than 3-5 metastatic lymph node metastases <1 cm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

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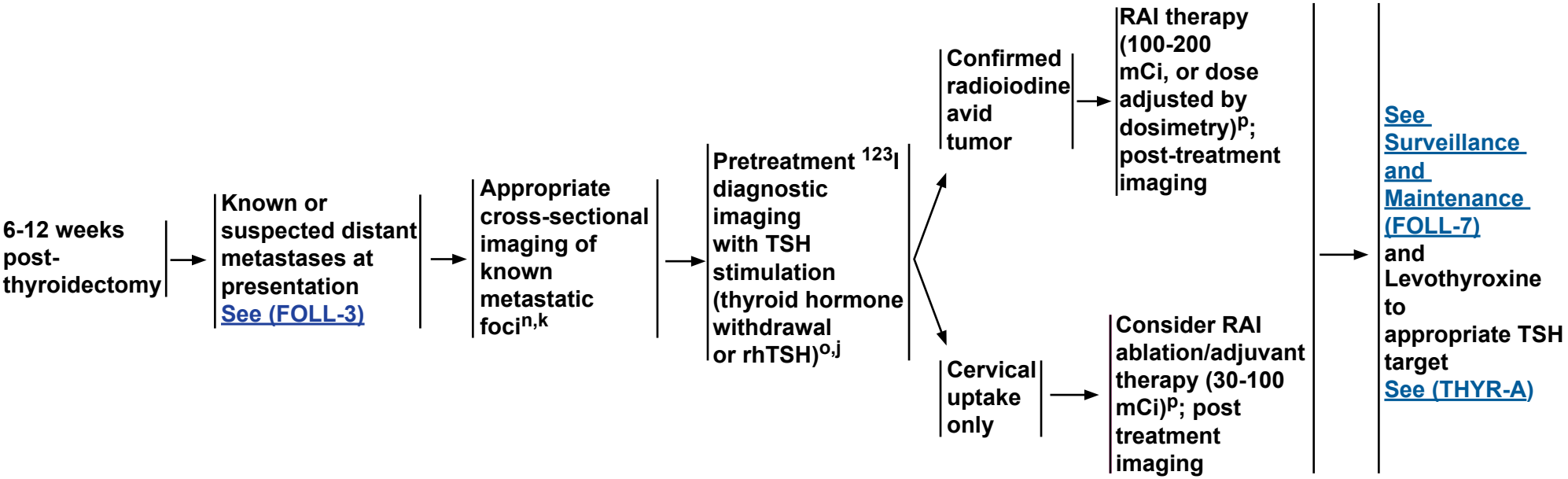
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[j]While pre-ablation diagnostic scans in this setting are commonly done at NCCN member institutions the panel recommends (category 2B) selective use of pre- ablation diagnostic scans based on pathology, post-operative Tg, intra-operative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.

[k]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.)

[n]To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression of vital structures or pathological fracture either as a result of disease progression or TSH stimulation.

[o]If I-123 is not available, low-dose ^{131}I (1-3 mCi) may be used. Dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis

[p]The administered activity of RAI therapy should be adjusted for pediatric patients.

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound[q]
- Consider TSH stimulated Tg measurement in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[r]
- Consider TSH-stimulated radioiodine imaging in high-risk patients, patients with previous RAI avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance
- In iodine responsive tumors, if detectable Tg or distant metastases or soft tissue invasion on initial staging, radioiodine imaging every 12-24 mo until no clinically significant response is seen to RAI treatment (either withdrawal of thyroid hormone or rhTSH)[s]
- If ^{131}I imaging negative and stimulated Tg > 2-5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT, chest CT, FDG-PET/CT)
- Patients treated with ^{131}I ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulatedthyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

RECURRENT DISEASE

- Stimulated Tg 1-10 ng/mL
- Non-resectable tumors
- Non-radioiodine responsive

→ Suppress TSH with levothyroxine[e]

Locoregional recurrence →
Surgery (preferred) if resectable[t] and/or
Radioiodine treatment,[l] if radioiodine imaging positive and/or
RT, if radioiodine imaging negative

- Stimulated Tg > 10 ng/mL and rising
- Scans (including PET) negative

→ Consider radioiodine therapy with 100-150 mCi[l] and post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

Metastatic disease → See Treatment of Metastases (FOLL-6)

[e] See Principles of TSH Suppression (THYR-A).
[l] The administered activity of RAI therapy should be adjusted for pediatric patients.
[q] A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[r] In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging. With a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).
[s] If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.
[t] Preoperative vocal cord assessment, if central neck recurrence.

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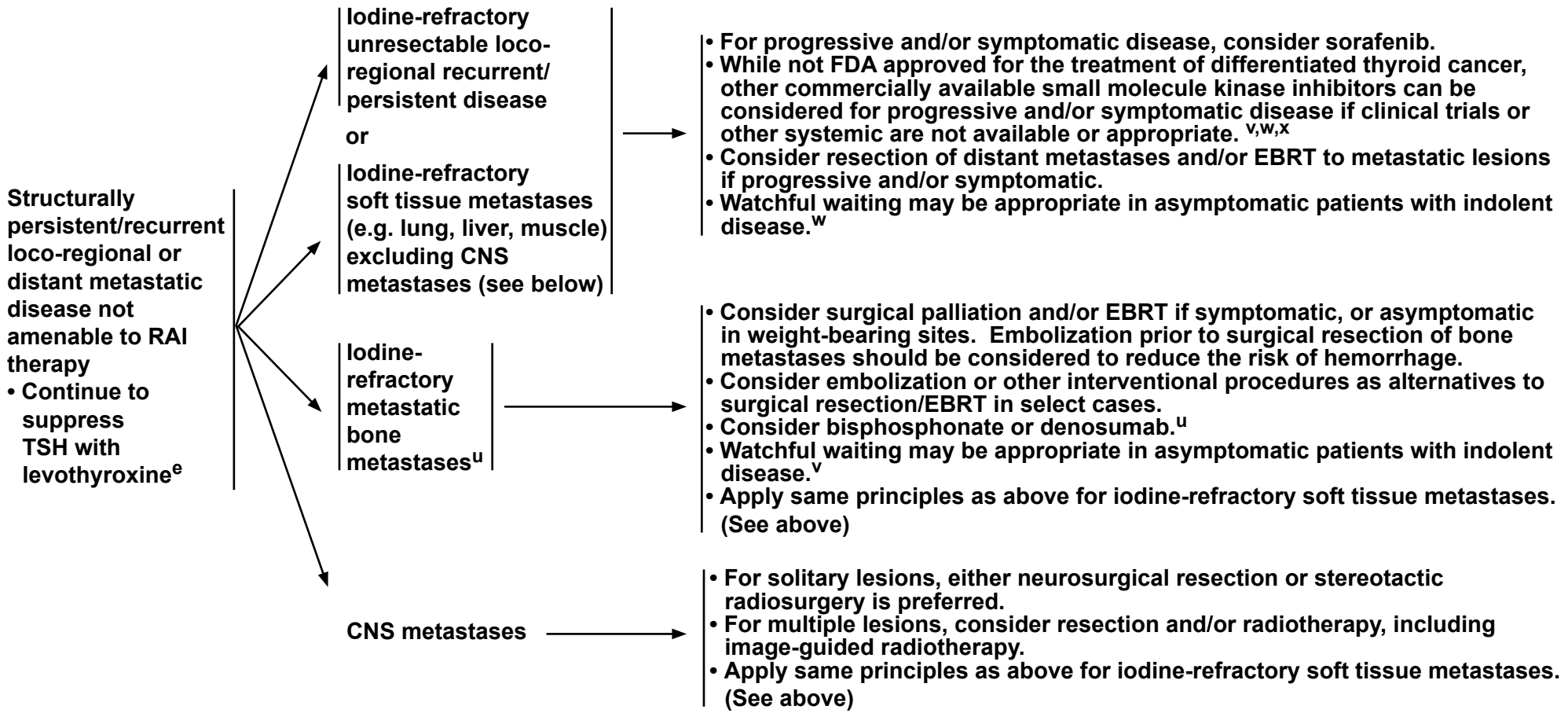
TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



[e] See Principles of TSH Suppression (THYR-A).
[u] Denosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[v] Kinase inhibitor therapy may not be approriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer (THYR-B)
[w] While not FDA approved for treatment of differentiated thyroid cancer, commercially available small molecule kinase inhibitors (such as axitinib, pazopanib, sunitinib, or vandetanib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[x] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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Thyroid Carcinoma – Hürthle Cell Carcinoma

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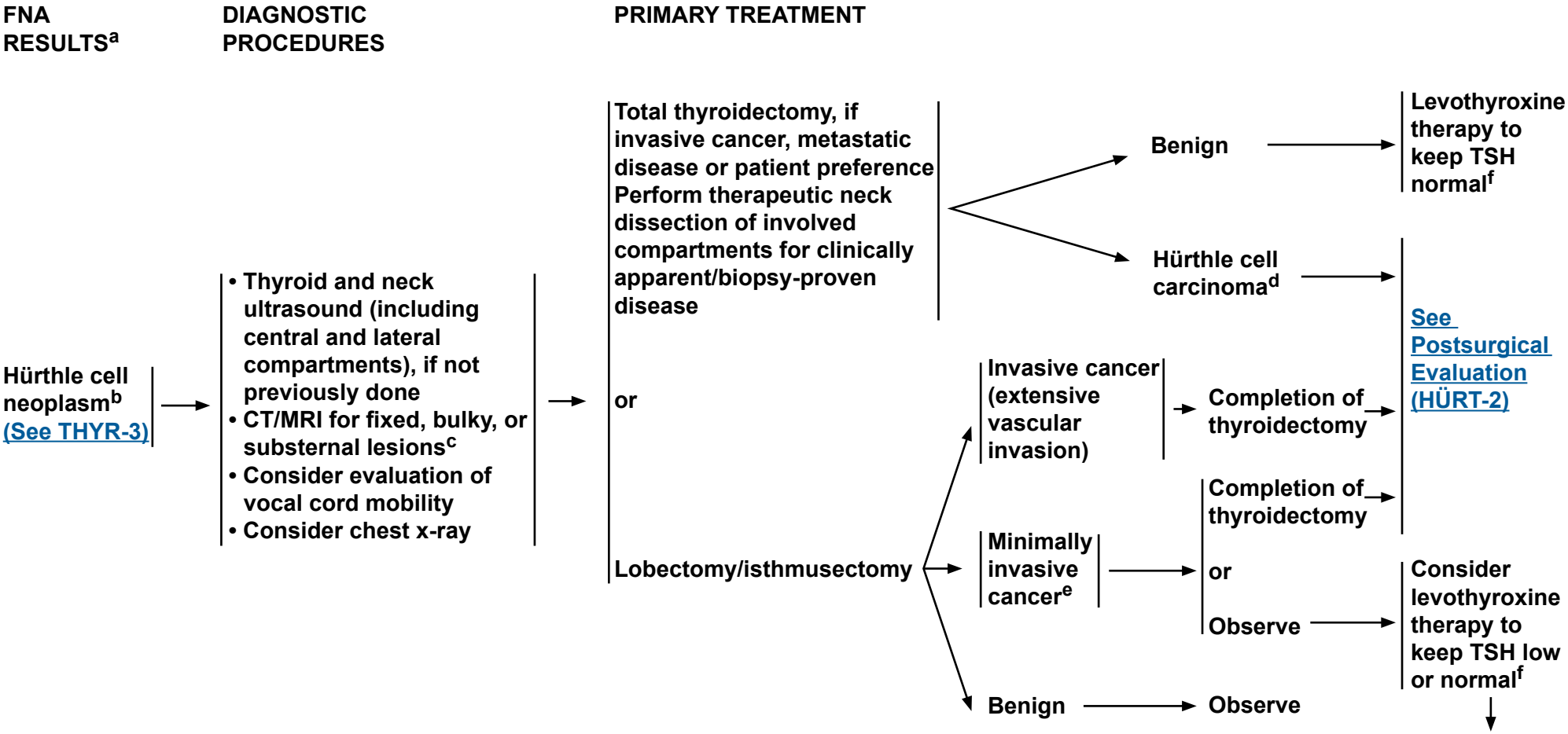

[a] See (ST-1) for staging.
[b] The diagnosis of Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA.
[c] Use of iodinated contrast will delay treatment with RAI but is required for optimal cervical imaging using CT.
[d] Also known as oxyphilic, oncocytic, or follicular carcinoma, oncocytic type.
[e] Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.
[f] See Principles of TSH Suppression (THYR-A).

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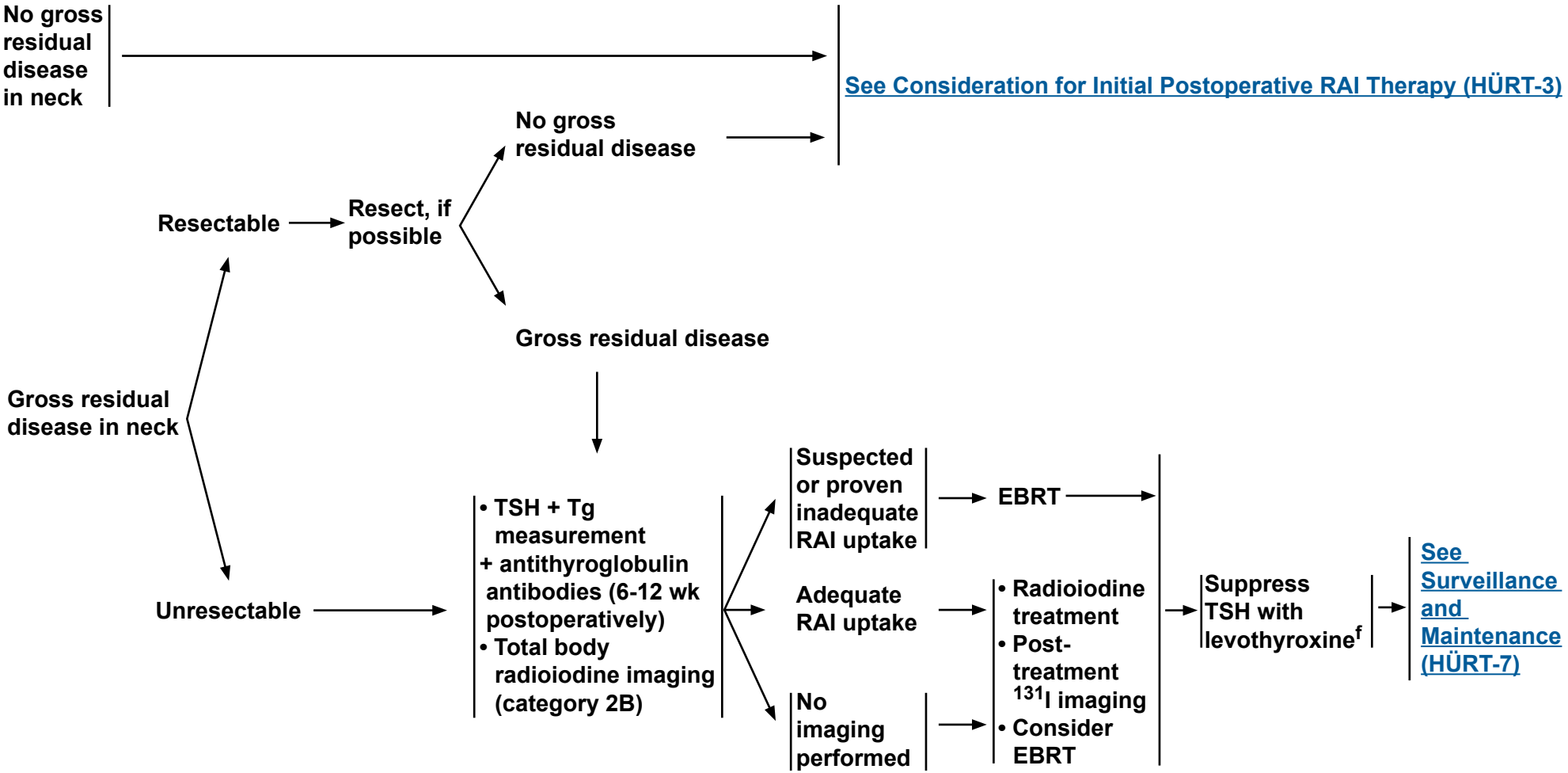
POSTSURGICAL EVALUATION



[f] See Principles of TSH Suppression (THYR-A).

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Thyroid Carcinoma – Hürthle Cell Carcinoma

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CLINICOPATHOLOGIC FACTORS

CONSIDERATION FOR INITIAL POSTOPERATIVE RAI THERAPY

RAI not typically recommended (if all present):
- **Primary tumor <2cm**
- **Intrathyroidal**
- **No vascular invasion**
- **Clinical N0, M0**
- **No detectable anti-Tg antibodies**
- **Postoperative unstimulated Tg <1 ng/mL[g]**

→ **RAI not typically indicated** See HÜRT-4

RAI selectively recommended (if any present):
- **Primary tumor 2-4 cm**
- **Minor vascular invasion**
- **Cervical lymph node metastases**
- **Presence of anti-Tg antibodies**
- **Postoperative unstimulated Tg <5-10 ng/mL[g]**

→ **RAI ablation is not required for minimally invasive Hürthle cell carcinoma confined to the thyroid when the primary tumor is small and demonstrates only invasion of the tumor capsule without vascular invasion** → **RAI not typically indicated** See HÜRT-4

→ **RAI ablation is recommended when the combination of individual clinical factors (such as the size of the primary tumor, histology, degree of vascular invasion, lymph node metastases, postoperative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.** → **RAI being considered** See HÜRT-5

RAI recommended (if any present):
- **Gross extrathyroidal extension**
- **Primary tumor > 4 cm**
- **Extensive vascular invasion**
- **Postoperative unstimulated Tg >5-10 ng/L[g,h]**

→ **RAI being considered** See HÜRT-5

Known or suspected distant metastases at presentation → **Amenable to RAI** See HÜRT-6

Gross residual disease not amenable to RAI therapy → See HÜRT-8

[g]Tg values obtained 6-12 weeks after total thyroidectomy.
[h]Additional cross sectional imaging should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

For general principles related to RAI therapy, See (Discussion)

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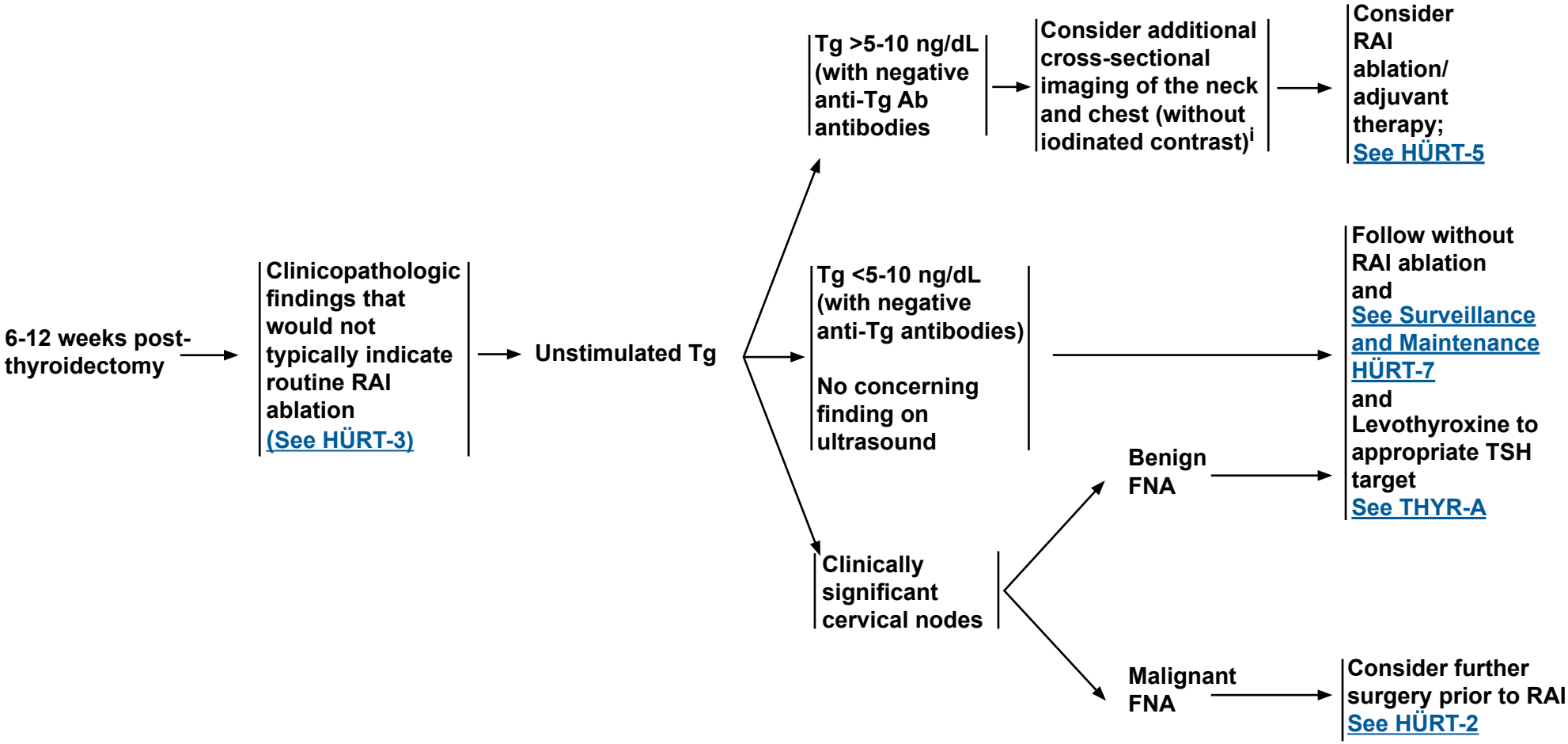

[i]If structural disease is identified, additional evaluation and/or treatment may be clinically indicated.

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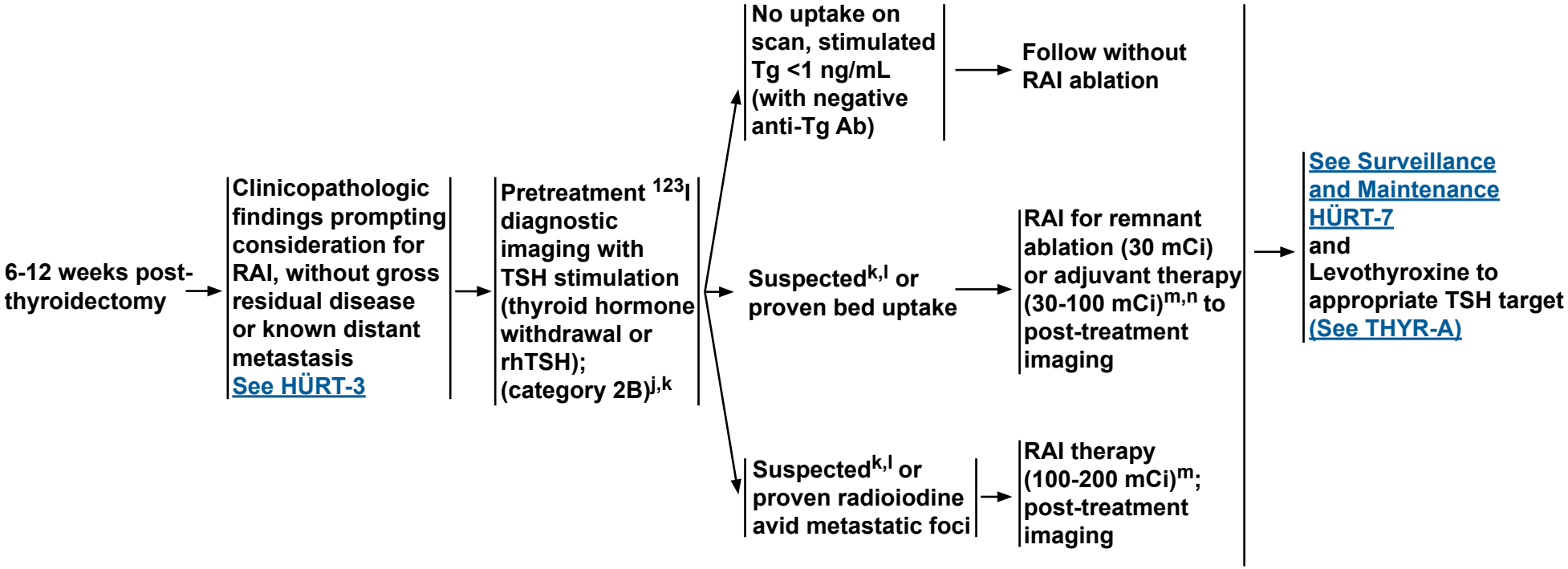

[j]Alternatively, low-dose ^{131}I (1-3 mCi) may be used.
[k]While pre-ablation diagnostic scans in this setting are commonly done at NCCN member institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, post-operative Tg, intra-operative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.
[l]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.
[m]The administered activity of RAI therapy should be adjusted for pediatric patients.
[n]If RAI ablation is used in T1b/T2 (1-4 cm), clinical N0 disease, 30 mCi of ^{131}I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This RAI ablation dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1-4 cm) with small-volume N1a disease (fewer than 3-5 metastatic lymph node metastases <1 cm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

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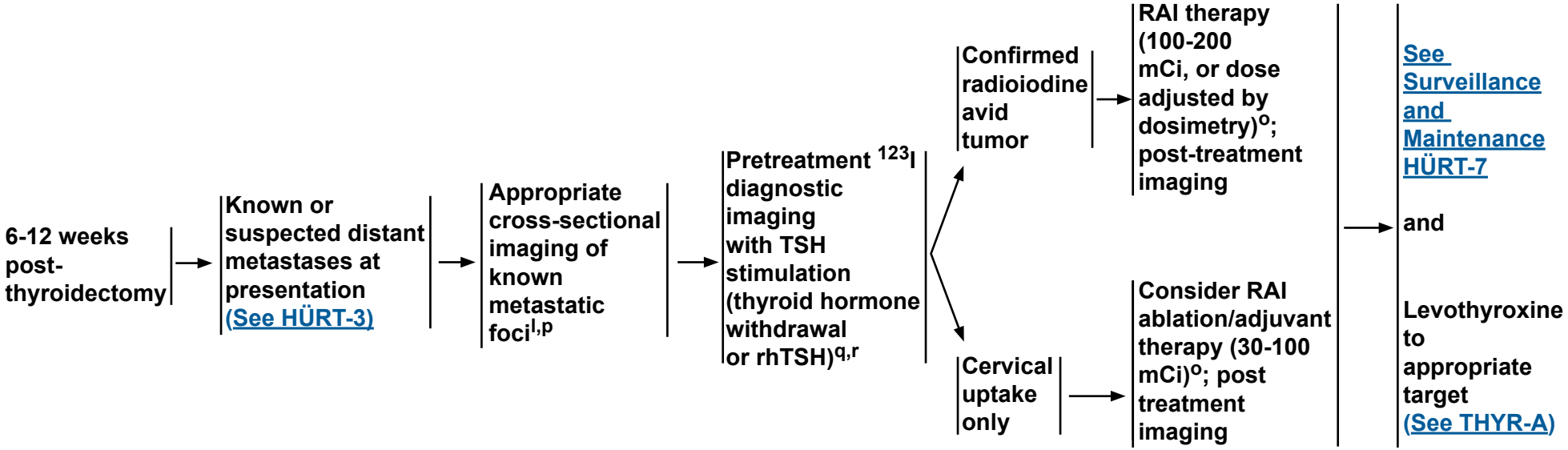
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[l]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.
[o]The administered activity of RAI therapy should be adjusted for pediatric patients.
[p]To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression.
[q]If ^{123}I is not available, low-dose ^{131}I(1-3 mCi) may be used. Dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis.
[r]While pre-ablation diagnostic scans in this setting are commonly done at NCCN member institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, post-operative Tg, intra-operative finds, and avaialble imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI avid distant metastasis of vital structures or pathological fracture either as a result of disease progression or TSH stimulation.

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SURVEILLANCE AND MAINTENANCE

- **Physical examination, TSH and Tg measurement + anti-thyroglobulin antibodies at 6 and 12 mo, then annually if disease free**
- **Periodic neck ultrasound[s]**
- **Consider TSH stimulated Tg measurement in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[t]**
- **Consider TSH-stimulated radioiodine imaging in high-risk patients, patients with previous RAI avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance**
- **In iodine responsive tumors, if detectable Tg or distant metastases or soft tissue invasion on initial staging, radioiodine imaging every 12-24 mo until no clinically significant response is seen to RAI treatment (either withdrawal of thyroid hormone or rhTSH)[u]**
- **If ^{131}I imaging negative and stimulated Tg > 2-5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT, chest CT, FDG-PET/CT)**
- **Patients treated with ^{131}I ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulated thyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging as clinically appropriate, may be considered if clinical suggestion of recurrent disease.**

RECURRENT DISEASE

- **Stimulated Tg 1-10 ng/mL**
- **Non-resectable tumors**
- **Non-radioiodine responsive**

→ **Suppress TSH with levothyroxine[f]**

Locoregional recurrence →
Surgery (preferred) if resectable[v] and/or
Radioiodine treatment,[o] if radioiodine imaging positive and/or
EBRT, if radioiodine imaging negative

- **Stimulated Tg > 10 ng/mL and rising**
- **Scans (including PET) negative**

→ **Consider radioiodine therapy with 100-150 mCi[o] and post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy**

Metastatic disease → **See Treatment of Metastatic Disease (HÜRT-8)**

[f] See Principles of TSH Suppression (THYR-A)
[o] The administered activity of RAI therapy should be adjusted for pediatric patients.
[s] A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[t] In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging. With a positive stimulated Tg, the concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).
[u] If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.
[v] Preoperative vocal cord assessment, if central neck recurrence.

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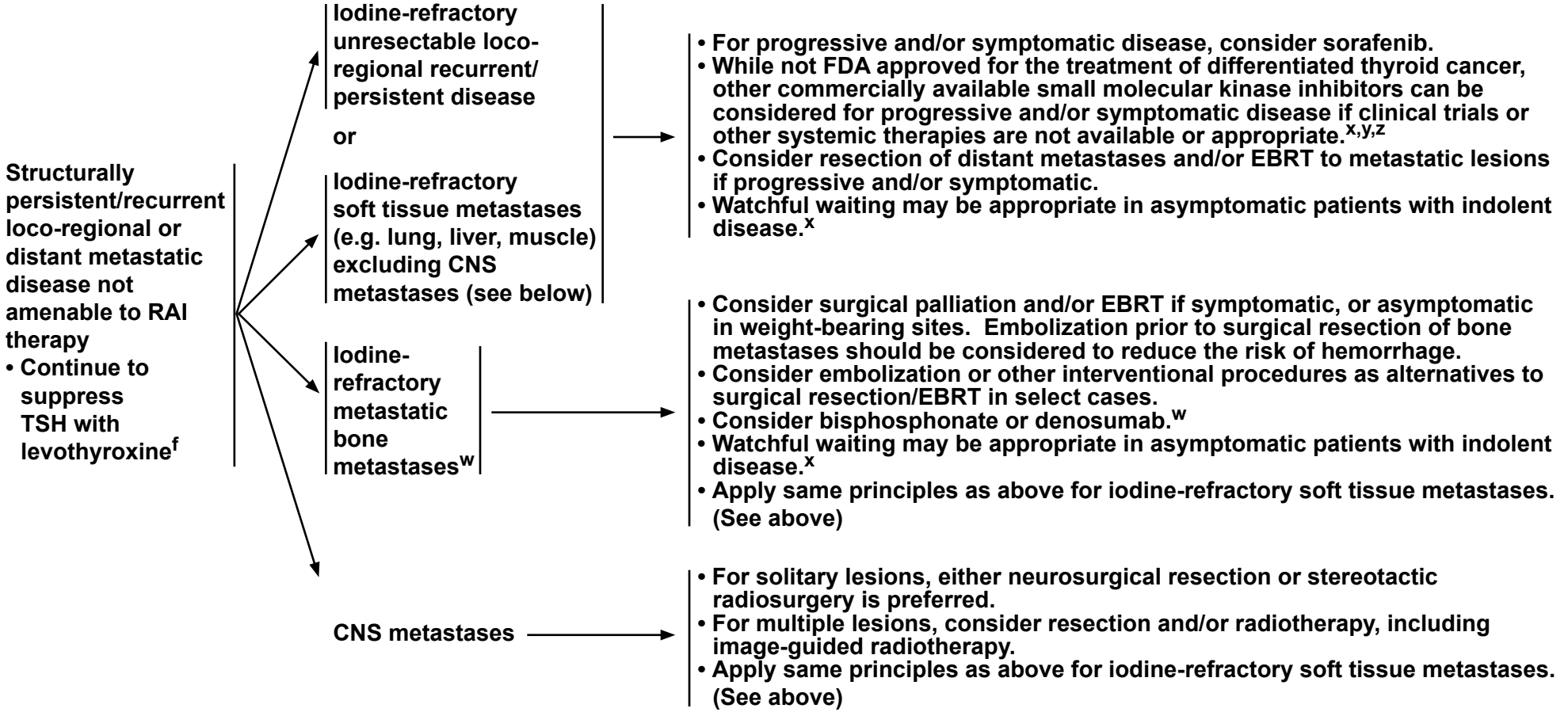
TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



[f] See Principles of TSH Suppression (THYR-A)

[w] Denosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

[x] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Therapy (THYR-B)

[y] While not FDA approved for treatment of differentiated thyroid cancer, commercially available small molecule kinase inhibitors (such as axitinib, pazopanib, sunitinib, or vandetanib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

[z] Cytotoxic chemotherapy has shown to have minimal efficacy, although most studies were small and underpowered.

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines Version 2.2014
Thyroid Carcinoma – Medullary Carcinoma

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CLINICAL PRESENTATION[a]

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT

Medullary thyroid carcinoma on FNA

- Basal serum calcitonin level
- CEA
- Pheochromocytoma screening[c]
- Serum calcium
- Consider genetic counseling
- Screen for RET proto-oncogene mutations[d] (exons 10, 11, 13-16)
- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- Consider evaluation of vocal cord mobility
- Consider contrast-enhanced CT of chest and mediastinum or MRI if N1 disease or calcitonin > 400 pg/mL

≥1.0 cm in diameter or bilateral thyroid disease

- Total thyroidectomy with bilateral central neck dissection (level VI)
- Therapeutic ipsilateral or bilateral modified neck dissection for clinically or radiologically identifiable disease (levels II–V)
- Consider prophylactic ipsilateral modified neck dissection for high volume or gross disease in the adjacent central neck
- Consider therapeutic EBRT for grossly incomplete tumor resection when additional attempts at surgical resection have been ruled out
- Consider adjuvant EBRT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate-to high-volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension
- Postoperative administration of levothyroxine to normalize TSH

< 1.0 cm in diameter and unilateral thyroid disease

Total thyroidectomy and consider neck dissection (level VI)

See Management 2-3 Months Postoperative (MEDU-5)

Medullary thyroid carcinoma diagnosed after initial thyroid surgery

See Additional Workup and Management (MEDU-2)

Germline mutation of RET proto-oncogene[b,c]

See Additional Workup and Primary Treatment (MEDU-3)

[a] See (ST-1) for staging.
[b] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[c] Evidence of pheochromocytoma should be evaluated and addressed appropriately before proceeding to the next step on the pathway.
[d] Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)

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

ADDITIONAL WORKUP

MANAGEMENT

Medullary thyroid carcinoma diagnosed after initial thyroid surgery[e]

- **Basal serum calcitonin level**
- **CEA**
- **Screen for RET proto-oncogene mutations[d] (exons 10, 11, 13-16)**
- **Consider genetic counseling**
- **Central and lateral neck compartments ultrasound, if not previously done**

RET positive → **See Additional Workup and Primary Treatment (MEDU-3)**

RET negative → **See Management 2-3 Months Postoperative (MEDU-5)**

[d]Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)

[e]If initial thyroid surgery was less than a total thyroidectomy, additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) is generally unnecessary unless a positive RET mutation or radiographic evidence of disease (ie, biopsy-proven residual neck disease).

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Thyroid Carcinoma – Medullary Carcinoma

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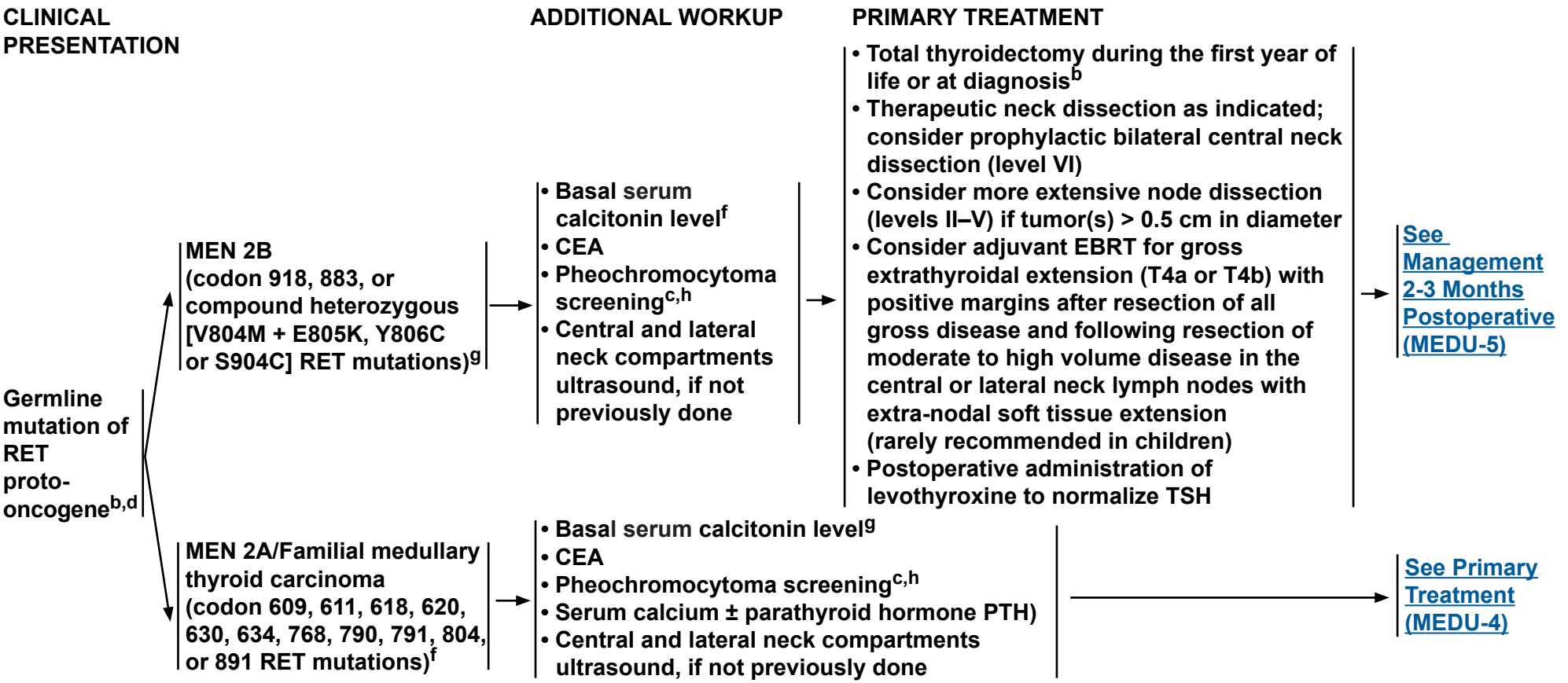

[b]In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[c]Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.
[d]Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)
[f]The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less high risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12)5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009; 19:565-612.).
[g]Normal calcitonin ranges have not been established for very young children.
[h]Screening for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A) should be performed annually. For some RET mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.

Note: All recommendations are category 2A unless otherwise indicated.
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Thyroid Carcinoma – Medullary Carcinoma

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CLINICAL PRESENTATION

PRIMARY TREATMENT

MEN 2A/Familial medullary thyroid carcinoma (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804 or 891 RET mutations)[b,d,f]

→ **Measure serum calcium ± PTH**

No primary hyperparathyroidism →

- **Total thyroidectomy by age 5[b,f] or when mutation identified[b] (if mutation identified at older age)**
- **Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin[i] or CEA test or ultrasound identified thyroid or nodal abnormality**
- **Consider prophylactic ipsilateral modified neck dissection if there is high volume or gross disease in the adjacent central neck**
- **Consider more extensive lymph node dissection (levels II–V) if tumor(s) > 1.0 cm or central node(s) positive**
- **Consider adjuvant EBRT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate to high volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension (rarely recommended in children)**
- **Postoperative administration of levothyroxine to normalize TSH**

→ **See Management 2-3 Months Postoperative (MEDU-5)**

Primary hyperparathyroidism →

- **See Primary Treatment as outlined above**
- **During primary operative procedure and parathyroid exploration:**
  - **If single adenoma, excise**
  - **If multiglandular disease, autotransplant or leave the equivalent mass of one normal parathyroid gland**
  - **Consider cryopreservation of parathyroid tissue**

→ **See Management 2-3 Months Postoperative (MEDU-5)**

[b]In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[d]Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)
[f]The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less high risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12)5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009; 19:565-612.).
[i]Prophylactic neck dissection may not be required if serum calcitonin is less than 40 ng/mL, because lymph node metastases are unlikely with minor calcitonin elevations in this setting.

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Thyroid Carcinoma – Medullary Carcinoma

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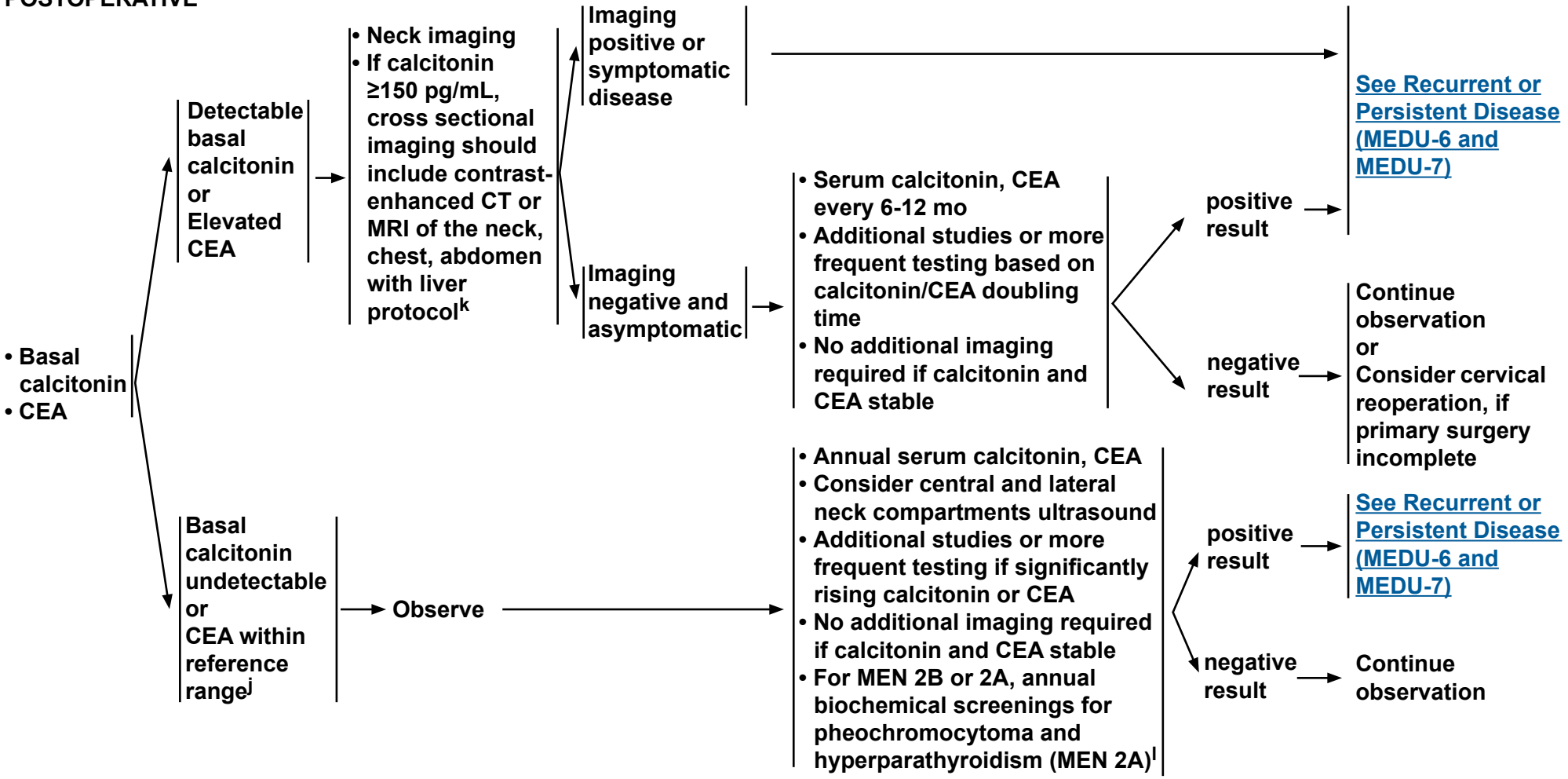
MANAGEMENT
2-3 MONTHS POSTOPERATIVE

SURVEILLANCE



[j]The likelihood of significant residual disease with an undetectable basal calcitonin is very low.
[k]Bone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.
[l]See page (PHEO-I) from the NCCN Guidelines for Neuroendocrine Tumors)

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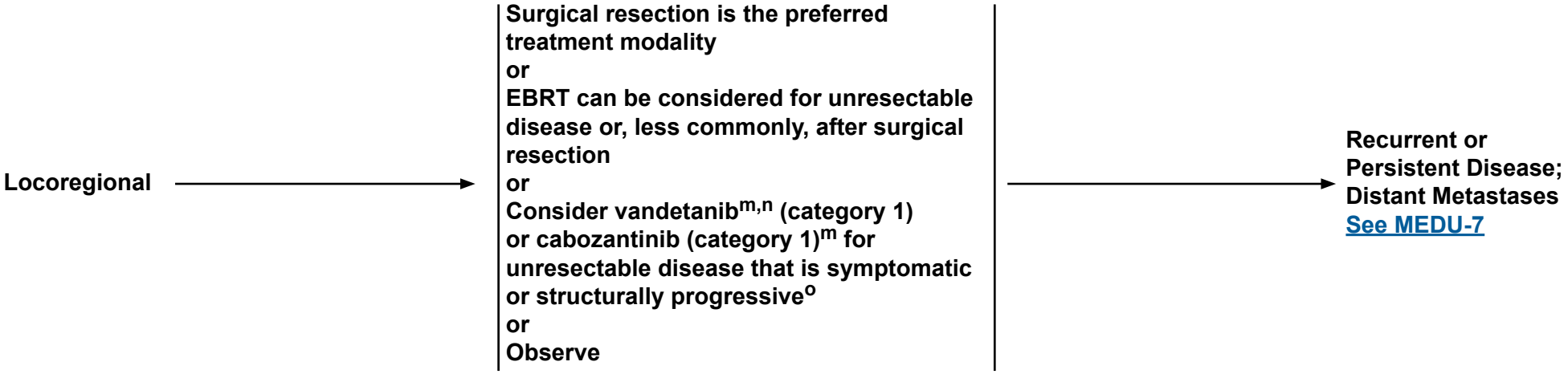
RECURRENT OR PERSISTENT DISEASE
Locoregional disease



[m]Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[n]Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.
[o]Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.
See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer (THYR-B).

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RECURRENT OR PERSISTENT DISEASE
DISTANT METASTASES

Asymptomatic disease →

Observe
or
Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy), or vandetanib[m,n] (category 1), or cabozantinib[m] (category 1) if not resectable and structurally progressive disease[p]

→ **Progressive disease, see pathway below**

Symptomatic disease or progression[p] →

- **Vandetanib (category 1)[q]**
  or
  Cabozantinib (category 1)[q]
  or
  Clinical trial
  or
  Consider other small molecule kinase inhibitors[r]
  or
  Dacarbazine (DTIC)-based chemotherapy

- **EBRT for focal symptoms**
- **Consider bisphosphonate or denosumab[s] therapy for bone metastases**
- **Consider palliative resection, ablation(eg, radiofrequency ablation [RFA], embolization, other regional therapy), or other regional treatment**
- **Best supportive care**

[m]Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[n]Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.
[p]Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer (THYR-B).
[q]Clinical benefit can be seen in both sporadic and familial MTC.
[r]While not FDA approved for treatment of medullary thyroid cancer, other commercially available small molecule kinase inhibitors (such as sorafenib or sunitinib) can be considered if clinical trials, vandetanib or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib.
[s]Denosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines Version 2.2014
Thyroid Carcinoma – Anaplastic Carcinoma

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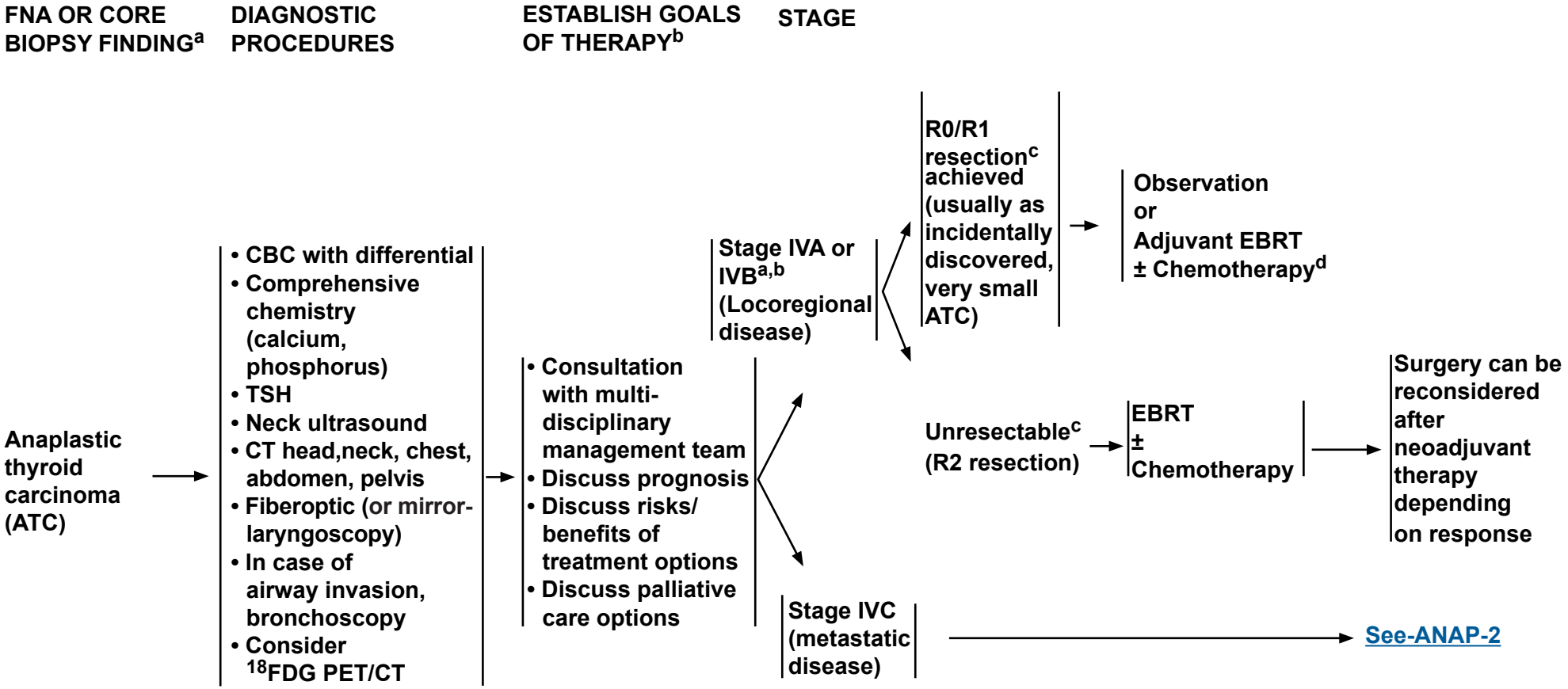

[a]Consider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary in order to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma and lymphoma.
[b]Preoperative evaluations need to be completed as quickly as possible and involve integrated decision making in a multidisciplinary team. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.
[c]Resectability for locoregional disease depends on extent of involved structures,potential morbidity, and mortality associated with resection. In most cases, there is no indication for a debulking surgery. See Staging (ST-1) for definitions of R0/R1/R2.
[d]See Systemic Therapy For Anaplastic Thyroid Carcinoma (ANAP-A).

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NCCN Guidelines Version 2.2014
Thyroid Carcinoma – Anaplastic Carcinoma

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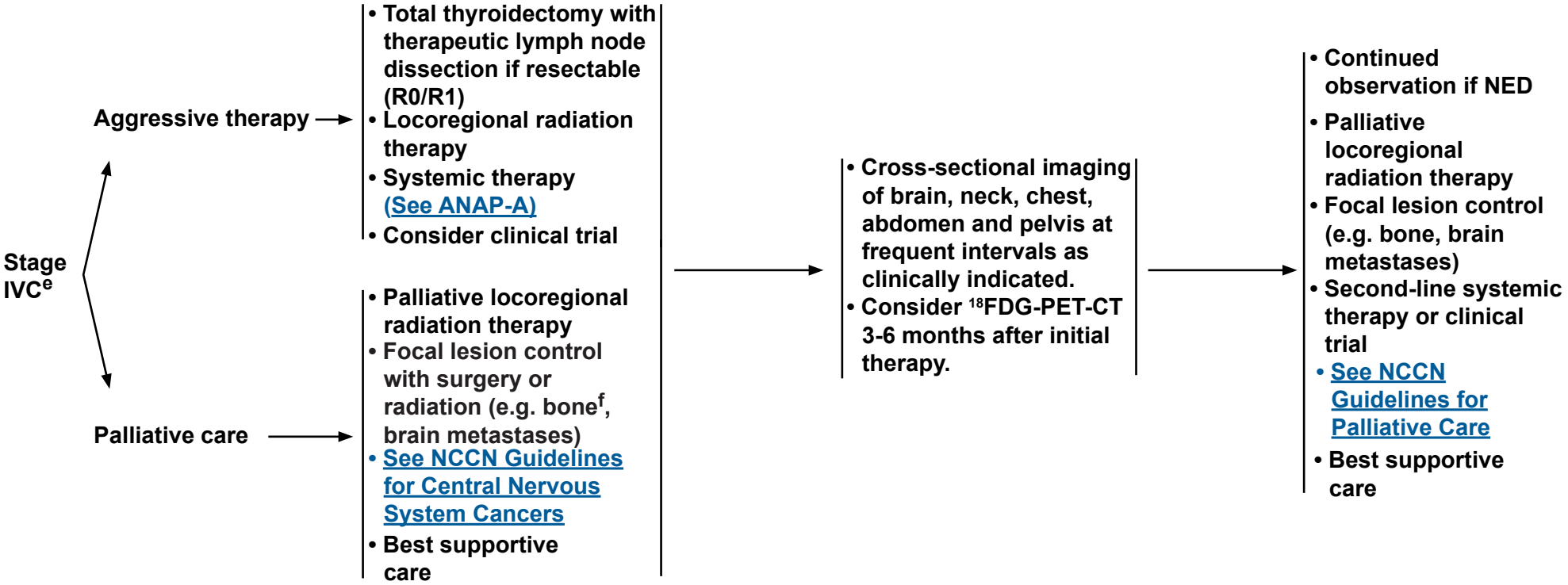
METASTATIC DISEASE

TREATMENT

SURVEILLANCE AND MANAGEMENT



[e]See Staging (ST-1) for staging.
[f]Consider use of bisphosphonates or denosumab. Denosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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SYSTEMIC THERAPY FOR ANAPLASTIC THYROID CARCINOMA

Concurrent Chemoradiation Regimens[1]
- **Paclitaxel/Carboplatin**
- **Paclitaxel**
- **Cisplatin**
- **Doxorubicin**

Chemotherapy Regimens[1]
- **Paclitaxel/Carboplatin**
- **Paclitaxel**[2]
- **Doxorubicin**[3]

[1]Smallridge RC, Ain KB, Asa SL, et al. American thyroid association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-1139.
[2]Ain KB, Egorin MJ, DeSimone PA.Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group.Thyroid 2000;10:587-594.
[3]Shimaoka K, Schoenfeld DA, DeWys WD, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985;56:2155-2160.

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NCCN Guidelines Version 2.2014 Staging
Thyroid Carcinoma

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Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging For Thyroid Cancer (7th ed., 2010)

Primary Tumor (T)
Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification).

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 2 cm or less in greatest dimension limited to the thyroid
T1a *Tumor 1 cm or less, limited to the thyroid*
T1b **T**umor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3 Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4a Moderately advanced diseaseTumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b Very advanced disease
Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel

All anaplastic carcinomas are considered T4 tumors.
T4a Intrathyroidal anaplastic carcinoma
T4b Anaplastic carcinoma with gross extrathyroid extension

Regional Lymph Nodes (N)
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
N1a Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Residual Tumor (R)
Classification of relevance to assess impact of surgery on outcomes:

R0 No residual tumor
R1 microscopic residual tumor
R2 macroscopic residual tumor
Rx presence of residual tumor cannot be determined

NCCN Guidelines Version 2.2014 Staging
Thyroid Carcinoma

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Stage grouping:
Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma.

Papillary or Follicular (differentiated)
Under 45 Years

Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1

Papillary or Follicular
45 Years and Older

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Medullary Carcinoma (all age groups)

Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Anaplastic Carcinoma
All anaplastic carcinomas are considered Stage IV

Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Histopathologic Type
There are four major histopathologic types:
- Papillary carcinoma (including follicular variant of papillary carcinoma)
- Follicular carcinoma (including Hürthle cell carcinoma)
- Medullary carcinoma
- Undifferentiated (anaplastic) carcinoma

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

Epidemiology

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the U.S. population for individuals ages 50 years and older.[1-3] Nodules are even more prevalent when the thyroid gland is examined at autopsy or surgery, or when using ultrasonography; 50% of the thyroids studied have nodules, which are almost always benign.[2,4] New nodules develop at a rate of about 0.1% per year, beginning in early life, but they develop at a much higher rate (approximately 2% per year) after exposure to head and neck irradiation.[5,6]

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is less than 1%.[7,8] It is estimated that approximately 62,980 new cases of thyroid carcinoma will be diagnosed in the United States in 2014.[9] As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men. With the incidence increasing every year,[10,11] thyroid carcinoma is currently the fifth most common malignancy diagnosed in women.[9] Among persons aged 15 to 24 years, thyroid carcinoma accounts for 7.5% to 10% of all diagnosed malignancies.[12-14] The disease is also diagnosed more often in white North Americans than in African Americans. Although thyroid carcinoma can occur at any age, the peak incidence is around age 49 years.[7,8]

The main histologic types of thyroid carcinoma include: 1) differentiated (including papillary, follicular, and Hürthle); 2) medullary; and 3) anaplastic (aggressive undifferentiated tumor). Of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, 80% had papillary carcinoma, 11% had follicular carcinoma, 3% had Hürthle cell carcinoma, 4% had medullary carcinoma, and 2% had anaplastic thyroid carcinoma.[15] The 10-year relative survival rates for patients with papillary, follicular, and Hürthle cell carcinomas were 93%, 85%, and 76%, respectively.[15]

In 2014, it is estimated that approximately 1890 cancer deaths will occur among persons with thyroid carcinoma in the United States.[9,16] Anaplastic thyroid carcinoma is almost uniformly lethal; however, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases. Although thyroid carcinoma occurs more often in women, mortality rates are lower for younger women.[7,8,17-19] The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004, but mortality rates decreased more than 44%.[8] From 1975 to 2004, thyroid cancer rates doubled in the United States.[20] From 1975 to 2009, thyroid cancer rates tripled mainly because of small papillary thyroid cancers.[21] Because overall mortality has remained stable since 1975, the increasing incidence may reflect earlier detection of subclinical disease (ie, small papillary cancers).[10,20-23] However, recent data show the incidence has increased by varying degrees across all tumor sizes.[24-28] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[16,29]

The *Summary of the Guidelines Updates* describes the most recent revisions in the algorithms, which have been incorporated into this updated Discussion text (see the NCCN Guidelines for Thyroid Carcinoma). For the 2014 update, a new section on kinase inhibitors was added (see *Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer* in the NCCN Guidelines for Thyroid Carcinoma). In addition, the guidelines for use of radioactive iodine (RAI) were extensively revised. By definition, the NCCN Guidelines cannot

incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the NCCN Panel during the process of developing these guidelines.

Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, Hürthle) thyroid carcinoma can be a challenge, because very few prospective randomized trials of treatment have been done.[30,31] Results from ongoing randomized trials will not be available for many years, given the typically prolonged course and relative infrequency of these tumors. Most of the information about treatment comes from studies of large cohorts of patients for whom therapy has not been randomly assigned. This accounts for much of the disagreement about managing differentiated carcinoma.

Nonetheless, most patients can be cured of this disease when properly treated by experienced physicians and surgeons.[32] The treatment of choice is surgery, whenever possible, followed by radioiodine (131I) in selected patients and thyroxine therapy in most patients.

Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma.[33] The thyroid glands of children are especially vulnerable to ionizing radiation. A child's thyroid gland has one of the highest risks of developing cancer of any organ. The thyroid gland is the only organ linked to risk at about 0.10 Gy.[5] The risk for radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma.[34] These data suggest that genetic factors are also important in the development of thyroid carcinoma. Beginning within 5 years of irradiation during childhood, new nodules develop at a rate of about 2% annually, reaching a peak incidence within 30 years of irradiation but remaining high at 40 years.[5,6]

Adults have a very small risk of developing thyroid carcinoma after exposure to 131I.[35] After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary thyroid carcinoma (PTC) after being exposed to 131I fallout.[36] It became evident that 131I and other short-lived 131Is were potent thyroid carcinogens in these children, particularly those younger than 10 years of age when they were exposed.[37] Iodine deficiency increases the risk for radiation-induced thyroid cancer.[38] Although radiation-induced PTC tends to appear more aggressive histologically and to have high recurrence rates, the prognosis for survival is similar to that of spontaneously occurring tumors.[39-41] Iodine deficiency is associated with follicular and anaplastic thyroid carcinomas.

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, Hürthle) thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. However, evaluating all nodules for malignancy is difficult, because benign nodules are so prevalent and because thyroid carcinoma is so uncommon.[1,42,43] Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their diagnosis. About 50% of the malignant nodules are discovered during a routine physical examination, by serendipity on imaging studies, or during surgery for benign disease. The other 50% are usually first noticed by the patient, usually as an asymptomatic nodule.[1,42] Regrettably, the typically indolent nature of differentiated thyroid carcinoma often leads to long delays in diagnosis that may substantially worsen the course of the disease.[19]

Initial Workup

For a patient with a thyroid nodule, the first step is to measure the serum thyrotropin (thyroid-stimulating hormone [TSH]) level and to do an ultrasound of the thyroid and central neck; all nodules (even incidentalomas) should have this assessment; there is no size cutoff.[3,44,45] Some NCCN Panel Members do not feel it is necessary to do an ultrasound of the lateral neck at this point, hence the category 2B recommendation (see box at the beginning of this Discussion for the explanation of the different categories). A category 2B recommendation means that many (>50%), but not all (<85%), of the NCCN Panel Members agree with the recommendation; the level of evidence (eg, phase II trial) is the same as for a category 2A recommendation. The TSH level, ultrasound results, and clinical features are used to determine whether is it necessary to do fine-needle aspiration (FNA) of the nodule or whether there is a low risk of malignancy (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[43,46]

FNA is the procedure of choice for evaluating suspicious thyroid nodules.[3,43,47] Data show that higher TSH levels are associated with an increased risk for differentiated thyroid carcinoma in patients with thyroid nodules, although TSH and thyroglobulin (Tg) do not appear to be useful for screening for thyroid cancer.[48-51] FNA should be considered in patients with normal or elevated TSH, certain ultrasound features, and clinical findings. FNA of suspicious cervical lymph nodes should also be considered if identified in the ultrasonographic evaluation of the thyroid and neck. Ultrasound features that increase the threshold for FNA are described in the NCCN algorithm (see *Sonographic Features* in *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). 131I imaging is recommended in patients with low TSH.

There is extensive literature that identifies ultrasound features that predict either benign or malignant thyroid nodules. Features examined include nodule size, relative echogenicity versus adjacent thyroid tissue, calcifications, border irregularity, a purely cystic content, mixed solid and cystic features, a variety of radiographic *signs*, increased internal vascularity, taller greater than wider nodules in the transverse measurement, a *spongiform* appearance, nodule elastography, and others. Ultrasound features associated with a low suspicion of malignancy include isoechoic or hyperechoic solid nodules; mixed solid/cystic nodules without microcalcification, irregular margins, or extrathyroidal extension; or spongiform nodules.[44,52-54] Efforts have been made to create standardized systems to improve consistency across centers.[53,55] Other than the presence of a pure cyst and nodule size, the inter-observer variability is reported to be high, making comparisons between centers challenging.[54] Nonetheless, a constellation of findings—such as a nodule with internal echogenicity consistent with microcalcifications, irregular borders, and increased internal vascularity—conveys a high risk of malignancy. Because size is a comparatively reproducible measure, its effect on likelihood of malignancy as an independent variable has been assessed. Two recent articles suggest that size is a relatively non-linear poor predictor of malignancy;[44,56] however, it may serve an important role in the setting of other concerning features.[57]

In the setting of a multinodular thyroid gland, selection of nodules for FNA should be based on the pattern of radiographic features that predict a higher likelihood of malignancy, such as the previous example, or based on growth of a nodule over time. Similarly, choosing which nodules are appropriate for monitoring rather than FNA should be based on the pattern of ultrasound features that predict benignity (eg, *spongiform* appearance, a pure cyst, or specific intranodular

appearances) or small size due to treatment considerations as previously noted.[52,53,58] At the time of thyroid ultrasound, a critical feature that should be assessed is the presence or absence of concerning lymphadenopathy in the central and lateral neck. The presence of a node with concerning characteristics should lead to FNA of the node rather than, or in addition to, the most concerning thyroid nodule.

Thyroid nodules smaller than 1 cm occur with such frequency in the asymptomatic general population that they are often found by serendipity when performing imaging studies for other head or neck problems.[22] Often termed *incidentalomas,* nodules smaller than 1 cm are typically clinically insignificant lesions and usually do not require FNA, unless there are suspicious findings (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[4,44,59-62] However, it may be appropriate to evaluate patients with high-risk clinical features (eg, radiation exposure, history of thyroid cancer, multiple first-degree relatives with thyroid cancer), which are described later in this section.[3,59,63] In selected cases, it may be reasonable to follow these nodules with serial ultrasounds. However, recent data indicate that older patients with intrathyroidal papillary microcarcinomas may be good candidates for an active surveillance approach (rather than immediate surgery) and usually show no evidence of clinically significant disease progression over at least 5 to 10 years of follow-up.[64] These observations cast doubt on the clinical benefit of diagnosing (and treating) papillary microcarcinoma in these selected groups.

The NCCN Panel uses recommendations from several organizations (eg, American Thyroid Association [ATA], Society of Radiologists in Ultrasound, NCI) and their expertise when formulating the NCCN Guidelines for thyroid nodules (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[3,46,65] The NCCN recommendations describe which nodules require further assessment with FNA and which can be observed. In 2009, the ATA updated its guidelines on the management of thyroid nodules and thyroid cancer; its comprehensive guidelines also discuss ultrasound and FNA.[3] In 2007, the NCI had a conference on using FNA to manage thyroid nodules. The NCI guidelines discuss which nodules should undergo FNA and discuss the FNA results (ie, carcinoma, benign).[43,46] The Society of Radiologists in Ultrasound wrote a consensus statement in 2005 about management of thyroid nodules identified at thyroid ultrasonography. Their recommendations describe which nodules should undergo FNA based on nodule size and ultrasound characteristics, and on clinical features that might predict risk of morbidity from an undiagnosed malignancy.[65] Suspicious criteria by ultrasound include increased central hypervascularity, hypoechoic mass, microcalcifications, infiltrative margins, and other features (see *Sonographic Features* in *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[66,67] For example, the likelihood that a nodule is malignant increases about 7-fold if it is very firm, fixed to adjacent structures, rapidly growing, associated with enlarged regional lymph nodes, causes vocal cord paralysis, or if symptoms of invasion into neck structures are present.[67,68] Family history of thyroid cancer is also indicative of malignancy. If 2 or more of these features are present, the likelihood of thyroid cancer is virtually assured; however, this is a rare situation.[68] A patient's age and gender also affect the probability of malignancy. Other factors that increase the suspicion of malignancy include: 1) a history of head and neck irradiation; 2) a history of diseases associated with thyroid carcinoma, such as familial adenomatous polyposis (formerly called Gardner's

syndrome), Carney complex, Cowden's syndrome, and multiple endocrine neoplasia (MEN) types 2A or 2B; 3) evidence of other thyroid cancer–associated diseases or syndromes, such as hyperparathyroidism, pheochromocytoma, marfanoid habitus, and mucosal neuromas (suggestive of MEN2B), which make the presence of medullary thyroid carcinoma (MTC) more likely; or 4) the presence of suspicious findings detected by imaging, such as focal FDG uptake on PET, or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.[3,69]

Some clinicians, especially in Europe,[70] recommend obtaining serum calcitonin levels from all patients with thyroid nodules to assess for MTC. However, this is controversial in the United States, especially in the absence of confirmatory pentagastrin stimulation testing and because it may not be cost effective. The ATA is equivocal about measuring serum calcitonin.[3] A recent study showed that calcitonin screening may be cost effective in the United States.[71] However, false-positive calcitonin readings that can result from minimal calcitonin elevations have traditionally been ruled out with pentagastrin testing, and pentagastrin is not available in the United States. Some authors have suggested high-dose calcium infusion as an alternative to pentagastrin stimulation testing in patients with minimal calcitonin elevations.[72]

FNA Results

Cytologic examination of an FNA specimen is typically categorized as: 1) carcinoma (papillary, medullary, or anaplastic) or suspicious for carcinoma; 2) follicular or Hürthle cell neoplasm; 3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); 4) thyroid lymphoma; 5) benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis); or 6) insufficient biopsy (nondiagnostic) (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). These diagnostic categories for FNA results reflect the NCI's state of the science conference held in 2007.[43,46] Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in the diagnosis of thyroid disorders. Although FNA is a very sensitive test—particularly for PTC —false-negative results are sometimes obtained; therefore, a reassuring FNA should not override worrisome clinical findings.[73,74]

Molecular diagnostic testing to detect individual mutations (eg, BRAF, RET/PTC, RAS, PAX8/PPAR [peroxisome proliferator-activated receptors] gamma) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions.[75-82] The choice of the precise molecular test depends on the cytology and the clinical question being asked.[83-86] Indeterminate groups include: 1) follicular or Hürthle cell neoplasms; and 2) AUS/FLUS.[87-89] The NCCN Panel recommends (category 2B) molecular diagnostic testing for evaluating FNA results that are suspicious for: 1) follicular or Hürthle cell neoplasms; or 2) AUS/FLUS (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[90,91] For the 2014 update, the NCCN Panel revised the recommendation for molecular diagnostic testing to category 2B for indeterminate FNA results based on a series of panel votes. The panel noted that molecular testing (both the *Gene Expression Classifier* and individual mutational analysis) was available in the majority of NCCN Member Institutions (>75%). About 70% of the panelists would recommend using a *gene expression classifier* in the evaluation of follicular lesions. The gene expression classifier measures the expression of at least 140 genes.[75,92,93] BRAF mutation analysis was recommended by 50% of the panelist in the evaluation of thyroid

nodules (not restricted to the follicular lesions). Furthermore, about 60% of the panelists would recommend BRAF testing in the evaluation of follicular lesions. A minority of panelists expressed concern regarding observation of follicular lesions because they were perceived as potentially pre-malignant lesions with a very low, but unknown, malignant potential if not surgically resected (leading to a recommendation for either observation or definitive surgical resection in lesions classified as benign by molecular testing) (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Rather than proceeding to immediate surgical resection to obtain a definitive diagnosis for these indeterminate FNA cytology groups (follicular lesions), patients can be followed with observation if the application of a specific molecular diagnostic test results in a predicted risk of malignancy that is comparable to the rate seen in cytologically benign thyroid FNAs (approximately ≤5%). It is important to note that the predictive value of molecular diagnostics may be significantly influenced by the pre-test probability of disease associated with the various FNA cytology groups. Furthermore, in the cytologically indeterminate groups, the risk of malignancy for FNA can vary widely between institutions.[94-97] Because the published studies have focused primarily on adult patients with thyroid nodules, the diagnostic utility of molecular diagnostics in pediatric patients remains to be defined. Therefore, proper implementation of molecular diagnostics into clinical care requires an understanding of both the performance characteristics of the specific molecular test and its clinical meaning across a range of pre-test disease probabilities.[91,98]

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of MTC.[46] Hürthle cell neoplasms can sometimes mimic MTC cytologically and on frozen section. Sometimes it can be difficult to discriminate between anaplastic thyroid carcinoma and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[99] Metastatic renal carcinoma can mimic a follicular neoplasm, melanoma can mimic MTC, and metastatic lung cancer can mimic anaplastic thyroid carcinoma.[46]

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens, such as those from the College of American Pathologists (CAP). The CAP protocol information and checklists—which were updated in June 2012 and reflect the 2010 staging (7th edition) from the AJCC—may be useful.

Follicular and Hürthle cell carcinomas are rarely diagnosed on FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.[32,43,73,100] Nodules that yield an abundance of follicular cells with little or no colloid are nearly impossible to categorize as benign or malignant on the basis of FNA.[101] Approximately 20% of these lesions are malignant.[67] Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[66,91,102]

In some patients with follicular lesions, serum TSH level and thyroid 123I or 99m technetium scanning may identify patients with an autonomously functioning or *hot* nodule who often may be spared surgery, because the diagnosis of follicular adenoma (ie, benign) is highly likely.[3,103] Patients who are clinically euthyroid with a low TSH and a hot nodule on thyroid imaging should be evaluated and treated for thyrotoxicosis as indicated even when cytology is suspicious for follicular neoplasm. Those with a *cold* or warm nodule and with suspicious clinical and sonographic features should proceed to surgery (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid

Carcinoma).[2,3] Those patients with a high or normal TSH and with cytology suspicious for follicular or Hürthle cell neoplasm should undergo diagnostic lobectomy or total thyroidectomy, depending on patient preference unless molecular diagnostic testing predicts a low risk of malignancy.

In patients with follicular or Hürthle cell neoplasm on FNA who are selected for thyroid surgery in order to obtain a definitive diagnosis, total thyroidectomy is recommended for bilateral disease, unilateral disease greater than 4 cm (especially in men), invasive cancer, metastatic cancer, or if the patient prefers this approach. An FNA that yields insufficient cellular material for diagnosis and is solid should be repeated, because approximately 50% of subsequent specimens are adequate to assign a diagnosis (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[67] Data suggest that ultrasound-guided FNA may be useful in diagnosing thyroid carcinoma, especially when repeating an FNA for a previously nondiagnostic biopsy.[3,104] In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.[105] Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of growth.[67] When a diagnosis of thyroid carcinoma is promptly established using FNA, the tumor is often confined to the thyroid or has metastasized only to regional nodes; thus, patients can be cured. However, as many as 5% of patients with papillary carcinoma and up to 10% of those patients with follicular or Hürthle cell carcinoma have tumors that aggressively invade structures in the neck or have produced distant metastases. Such cancers are difficult to cure.

Recurrence of Differentiated Thyroid Carcinoma

Depending on initial therapy and other prognostic variables, up to 30% of patients with differentiated thyroid carcinoma may have tumor recurrences during several decades; 66% of these recurrences occur within the first decade after initial therapy.[19] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[106,107] In one large study, central neck recurrences were seen most often in the cervical lymph nodes (74%), followed by the thyroid remnant (20%), and then the trachea or muscle (6%). Of the group with local recurrences, 8% eventually died of cancer.[19] Distant metastases were the sites of recurrence in 21% of patients in this cohort, most often (63%) in the lungs alone. Of the patients with distant metastases, 50% died of cancer.[19]

It is important to recognize that the poor outcomes in this study were probably related to the manner in which the recurrence was diagnosed. In the past, disease recurrence was heralded by symptoms or palpable disease on physical examination, reflecting relatively large-volume disease recurrence. However, tools that are highly sensitive for detecting disease (eg, sensitive Tg assays, high-resolution neck ultrasound) appear to have resulted in earlier detection of disease recurrence, which is now often found in the first 2 to 5 years of follow-up.[3,108] These non-palpable, small-volume lymph node recurrences often show little evidence of disease progression over many years and do not appear to be associated in an increase in mortality.[109,110]

Prognosis

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular thyroid carcinomas, patient age at the time of initial therapy and tumor stage are important.[19,111-113] Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in men. Thyroid carcinoma is more lethal in patients older than 40 years, increasingly so with each subsequent decade of

life. The mortality rate increases dramatically after age 60 years. However, tumor recurrence shows a remarkably different behavior with respect to age. Recurrence frequencies are highest (40%) for those younger than 20 years or older than 60 years; recurrence at other ages ensues in only about 20% of patients.[19,111-114] This disparity between cancer-related mortality and the frequency of tumor recurrence probably accounts for most of the disagreements among clinicians concerning optimal treatment for patients with differentiated thyroid carcinoma. How clinicians assess the importance of tumor recurrence (as opposed to cancer-specific survival) accounts for much of the debate surrounding the influence of age on the treatment plan for children and young adults.

Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good.[115,116] Although the prognosis of children with thyroid carcinoma is favorable for long-term survival (90% at 20 years), the standardized mortality ratio is 8-fold higher than predicted.[117] Some clinicians believe that young age imparts such a favorable influence on survival that it overshadows the behavior expected from the characteristics of the tumor. Therefore, they classify most thyroid tumors as low-risk tumors that may be treated with lobectomy alone.[118-120] However, most physicians treating the disease believe that tumor stage and its histologic features should be as significant as the patient's age in determining management.[19,115,121,122] Prognosis is less favorable in men than in women, but the difference is usually small.[19,120] One study found that gender was an independent prognostic variable for survival and that the risk of death from cancer was about twice as high in men as in women.[19] Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.[123]

Familial Syndromes

Familial, non-MTC accounts for about 5% of PTCs and, in some cases, may be clinically more aggressive than the sporadic form.[124,125] For patients to be considered as having familial PTC, most studies require at least 3 first-degree relatives to be diagnosed with PTC because the finding of cancer in a single first-degree relative may just be a chance event. Microscopic familial PTC tends to be multifocal and bilateral, often with vascular invasion, lymph node metastases, and high rates of recurrence and distant metastases.[126] Other familial syndromes associated with PTC are familial adenomatous polyposis,[127] Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands),[128] and Cowden's syndrome (multiple hamartomas).[129] The prognosis for patients with all of these syndromes is not different from the prognosis of those with spontaneously occurring PTC.

Tumor Variables Affecting Prognosis

Some tumor features have a profound influence on prognosis.[114,130-132] The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, BRAF mutation status, and metastases.[133,134] For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.[3,135-138] The CAP protocol provides definitions of vascular invasion and other terms. In patients with sporadic MTC, a somatic RET oncogene mutation confers an adverse prognosis.[139]

Histology

Although survival rates with typical PTC are quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors.[1] A well-defined tumor capsule, which is found in about 10% of PTCs, is a particularly favorable prognostic indicator. A worse prognosis

is associated with: 1) anaplastic tumor transformation; 2) tall-cell papillary variants, which have a 10-year mortality of up to 25%; 3) columnar variant papillary carcinoma (a rapidly growing tumor with a high mortality rate); and 4) diffuse sclerosing variants, which infiltrate the entire gland.[32,140] Follicular-variant PTC (FVPTC), which is recognized by its follicular architecture and typical papillary cytology, does not appear to have a worse prognosis than the pure papillary lesions if the FVPTC is encapsulated.[114,140-142] Molecular diagnostic testing is also useful for diagnosing FVPTC.[78]

Follicular thyroid carcinoma is typically a solitary encapsulated tumor that may be more aggressive than PTC. It usually has a microfollicular histologic pattern. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.[143] Many follicular thyroid carcinomas are minimally invasive tumors, exhibiting only slight tumor capsular penetration without vascular invasion. They closely resemble follicular adenomas and are less likely to produce distant metastases or to cause death.[144] FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.[43,100] Therefore, the tumor is often simply referred to as a *follicular neoplasm* by the cytopathologist (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[73] The diagnosis of follicular thyroid carcinoma is assigned only after diagnostic lobectomy or thyroidectomy and indeed only after analysis of the *permanent* histologic sections shows tumor capsule invasion by follicular cells.

Highly invasive follicular thyroid carcinomas are much less common; they are sometimes recognized at surgery by their invasion of surrounding tissues and extensive invasion of blood vessels. Up to 80% of these cancers metastasize, causing death in about 20% of patients, often within a few years of diagnosis.[114] The poor prognosis is closely related to older age at the time of diagnosis, advanced tumor stage, and larger tumor size.[19] The mortality rates for papillary and follicular thyroid carcinomas are similar in patients of comparable age and disease stage. Patients with either cancer have an excellent prognosis if the tumors are confined to the thyroid, are small, and are minimally invasive. However, patients with either papillary or follicular thyroid carcinoma have far less favorable outcomes if their disease is highly invasive or they develop distant metastases.[19,145]

When Hürthle (oncocytic) cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as Hürthle cell carcinoma, although the WHO classification and the AJCC consider it as a variant of follicular thyroid carcinoma.[146,147] Molecular studies suggest, however, that this tumor may be more similar to papillary than follicular thyroid carcinomas.[148,149] Benign and malignant Hürthle tumors usually cannot be discriminated by FNA or frozen section examination, although large (>4 cm) tumors are more likely to be malignant than smaller ones.[150] Similar to follicular thyroid carcinoma, the diagnosis of Hürthle cell carcinoma is only assigned after analysis of the *permanent* histologic sections (obtained from diagnostic lobectomy or thyroidectomy) shows tumor capsule invasion by Hürthle cells.

Hürthle cell carcinomas may be aggressive, especially when vascular invasion or large tumors occur in older patients.[151,152] In 2 large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, about twice the frequency of follicular thyroid carcinoma metastases.[153,154] In contrast to papillary or follicular carcinomas, 131I may be not effective in patients with Hürthle cell carcinoma because fewer Hürthle cell carcinomas concentrate 131I. In a series of 100 patients with distant metastases, 131I uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell

carcinomas.[155] In the National Cancer Data Base report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.[15]

Primary Tumor Size

PTCs smaller than 1 cm, termed *incidentalomas* or *microcarcinomas*, are typically found incidentally after surgery for benign thyroid conditions. Their cancer-specific mortality rates are near zero.[156] The risk of recurrence in papillary microcarcinomas ranges from 1% to 2% in unifocal papillary microcarcinomas, and from 4% to 6% in multifocal papillary microcarcinomas.[157,158] Other small PTCs become clinically apparent. For example, about 20% of microcarcinomas are multifocal tumors that commonly metastasize to cervical lymph nodes. Some researchers report a 60% rate of nodal metastases from multifocal microcarcinomas,[159] which may be the presenting feature and also may be associated with distant metastases.[156] Otherwise, small (<1.5 cm) papillary or follicular carcinomas confined to the thyroid almost never cause distant metastases. Furthermore, recurrence rates after 30 years are one third of those associated with larger tumors; 30-year cancer-specific mortality is 0.4% compared to 7% ($P < .001$) for tumors 1.5 cm or larger.[19] In fact, the prognosis for papillary and follicular thyroid carcinomas is incrementally poorer as tumors increase in size.[145,160] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas.[19]

Local Tumor Invasion

Up to 10% of differentiated thyroid carcinomas invade through the outer border of the gland and grow directly into surrounding tissues, increasing both morbidity and mortality. The local invasion may be microscopic or gross; it can occur with both papillary and follicular thyroid carcinomas.[19,161] Recurrence rates are 2 times higher with locally invasive tumors, and as many as 33% of patients with such tumors die of cancer within a decade.[19,162]

Lymph Node Metastases

In one review, nodal metastases were found in 36% of 8029 adults with PTC, in 17% of 1540 patients with follicular thyroid carcinoma, and in up to 80% of children with papillary carcinoma.[114] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[163] The prognostic importance of regional lymph node metastases is controversial.[3] However, an analysis of more than 9900 patients in the SEER database found a significant difference in survival at 14 years for those with and without lymph node metastases (79% vs. 82%, respectively).[164] Older patients (>45 years) with PTC and lymph node metastases also have decreased survival.[165] A recent review by Randolph et al emphasized the correlation between the size and number of metastatic lymph nodes and the risk of recurrence.[166] Identification of fewer than 5 sub-cm metastatic lymph nodes was associated with a low risk of recurrence. Conversely, structural disease recurrence rates of more than 20% to 30% were seen in large-volume lymph node metastases (>3 cm, or >5–10 involved lymph nodes).

Distant Metastases

Distant metastases are the principal cause of death from papillary and follicular thyroid carcinomas.[167,168] Almost 10% of patients with papillary carcinoma and up to 25% of those with follicular thyroid carcinoma develop distant metastases. About 50% of these metastases are present at the time of diagnosis.[114] Distant metastases occur even more often in patients with Hürthle cell cancer (35%) and in those patients who are older than age 40 years at diagnosis.[153,155] Among 1231 patients in 13 studies, the sites of reported distant metastases were lung (49%), bone (25%), both lung and bone (15%), and the central

nervous system (CNS) or other soft tissues (10%). The main predictors of outcome for patients with distant metastases are patient's age, the site of the distant metastasis, whether the metastases concentrate 131I, and morphology on chest radiograph.[153,155,169,170]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[114] Even so, some pulmonary metastases are compatible with long-term survival.[171] For example, one study found that when distant metastases were confined to the lung, more than 50% of the patients were alive and free of disease at 10 years, whereas no patients with skeletal metastases survived that long.[172] The survival rates are highest in young patients with diffuse lung metastases seen only on 131I imaging and not on x-ray.[170,172,173] Prognosis is worse with large pulmonary metastases that do not concentrate 131I.[153,155,169]

Tumor Staging

The NCCN Guidelines for Thyroid Carcinoma do not use TNM stages as the primary determinant of management. Instead, many characteristics of the tumor and patient play important roles in these NCCN Guidelines. Many specialists in thyroid cancer also follow this paradigm. When treating differentiated thyroid carcinoma, where most patients do not die, many clinicians place a stronger emphasis on potential morbidity than on mortality (see *Surgical Complications* in this Discussion). Staging was revised in the 2002 AJCC guidelines (6th edition) for patients with papillary and follicular thyroid carcinomas who are older than 45 years.[174] Note that the AJCC considers Hürthle cell carcinoma as a variant of follicular carcinoma, as does the WHO.[146] In the current 2010 AJCC staging guidelines (7th edition), T1 is divided into T1a and T1b (see Table 1).[146] In addition, the term *moderately advanced* is now used instead of *resectable* and the term *very advanced* is used instead of *unresectable*. Many studies (including those described in this Discussion) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[175] and not the 6th or 7th editions.[146,174]

Prognostic Scoring Strategies

Several staging and clinical prognostic scoring strategies use patient age older than 40 years as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma.[112,118,146,174,176] These strategies include the EORTC, TNM 7th edition, AMES (Age, Metastases, Extent, and Size), and AGES (Age, tumor Grade, Extent, and Size). All of these strategies effectively distinguish between patients at low and high risk.[160] With incrementally worsening MACIS (Metastasis, Age, Completeness of resection, Invasion, and Size) scores of less than 6, 6 to 6.99, 7 to 7.99, and 8+, however, the 20-year survival rates were 99%, 89%, 56%, and 24%, respectively.[118]

Unfortunately, a study that classified 269 patients with PTC according to 5 different prognostic paradigms found that some patients in the lowest-risk group from each approach died of cancer.[121] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[174,177] The AJCC TNM staging approach (see Table 1), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 45 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,[178,179] TNM staging was not established as a predictor of recurrence and therefore does not accurately forecast the recurrences that often occur in patients who developed thyroid carcinoma when they were young. Two studies have shown the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.[112,180]

A three-tiered staging system (low, intermediate, high) that uses clinicopathologic features to risk stratify with regard to the risk of recurrence has recently been suggested and validated.[3,181-184] This staging system effectively risk stratifies patients with regard to the risk of recurrence, risk of persistent disease after initial therapy, risk of having persistent structural disease, likelihood of achieving remission in response to initial therapy, and likelihood of being in remission at final follow-up. More recently, emphasis has been placed on evaluation of response to therapy using a dynamic risk assessment approach in which the initial risk estimates are modified during follow-up as additional data are accumulated.[185] This allows ongoing re-assessment of risk and allows the management paradigm to be better tailored to realistic estimates of risk that may change substantially over time.

Surgical Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total Thyroidectomy

The appropriate extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk PTC, which is reflected in the NCCN category 2B recommendations for these procedures (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma and *Papillary Thyroid Carcinoma* in this Discussion). In most clinical settings, decisions about the extent of thyroidectomy should be individualized and done in consultation with the patient. Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring[120] and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic for low-risk PTCs (MACIS score ≤3.99) had no improvement in survival rates after undergoing procedures more extensive than ipsilateral lobectomy. Thus, the authors concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[186]

Cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy were assessed in patients with PTC considered to be low risk by AMES criteria.[187] No significant differences were found in cancer-specific mortality or distant metastasis rates between the 2 groups. However, the 20-year frequencies of local recurrence and nodal metastasis after unilateral lobectomy were 14% and 19%, respectively, which were significantly higher (P = .0001) than the frequencies of 2% and 6% seen after bilateral thyroid lobe resection. Hay et al concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk PTC.[187]

Most NCCN Panel Members (and guidelines from the ATA) recommend total thyroidectomy for all patients in whom the diagnosis of PTC is assigned preoperatively,[3,32,188] because such procedures are associated with improved disease-free survival, even in children and adults with low-risk tumors.[106,122,187,189] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.[114,186] After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and 131I therapy)[19] and the highest frequency (11%) of subsequent pulmonary metastases.[190] However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.[39] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.[19]

However, some prominent thyroid cancer specialists (including some at NCCN Member Institutions) oppose this view and advocate unilateral lobectomy for most patients with papillary and follicular thyroid

carcinoma based on 1) the low mortality among most patients (ie, those patients categorized as low risk by the AMES and other prognostic classification schemes); and 2) the high complication rates reported with more extensive thyroidectomy.[119,176,191] The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole-body 131I imaging. Panel members recommend total lobectomy (without requiring RAI ablation) for patients with PTC who have small-volume pathologic N1 micrometastases (≤5 involved nodes, all <0.2 cm in largest dimension).[192]

NCCN Panel Members believe that total lobectomy alone is adequate treatment for papillary microcarcinomas provided the patient has not been exposed to radiation, has no other risk factors, and has a tumor smaller than 1 cm that is unifocal and confined to the thyroid without vascular invasion (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[19,156,193-196] Total lobectomy alone is also adequate treatment for minimally invasive follicular thyroid carcinomas (see *Primary Treatment* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

However, completion thyroidectomy is recommended for any of the following: tumor more than 4 cm in diameter, positive margins, gross extrathyroidal extension, macroscopic multifocal disease, macroscopic nodal metastases, confirmed contralateral disease, or vascular invasion.[3] Note that *gross extrathyroidal extension* refers to spread of the primary tumor outside of the thyroid capsule with invasion into the surrounding structures such as strap muscles, trachea, larynx, vasculature, esophagus, and/or recurrent laryngeal nerve.[133,197,198]

Completion Thyroidectomy

This procedure is recommended when remnant ablation is anticipated or if long-term follow-up is planned with serum Tg determinations and with (or without) whole-body 131I imaging. Large thyroid remnants are difficult to ablate with 131I.[190] Completion thyroidectomy has a complication rate similar to that of total thyroidectomy. Some experts recommend completion thyroidectomy for routine treatment of tumors 1 cm or larger, because approximately 50% of patients with cancers this size have additional cancer in the contralateral thyroid lobe.[161,199-205] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[202]

Miccoli et al studied irradiated children from Chernobyl who developed thyroid carcinoma and were treated by lobectomy; they found that 61% had unrecognized lung or lymph node metastases that could only be identified after completion thyroidectomy.[122] In another study, patients who underwent completion thyroidectomy within 6 months of their primary operation developed significantly fewer lymph node and hematogenous recurrences, and they survived significantly longer than did those in whom the second operation was delayed for more than 6 months.[203]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults[206] and children[122,207] undergoing total thyroidectomy. The rates of long-term recurrent laryngeal nerve injury and hypoparathyroidism, respectively, were 3% and 2.6% after total thyroidectomy and 1.9% and 0.2% after subtotal thyroidectomy.[208] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of

patients 1 year later.[209] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[210]

When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5860 patients found that surgeons who performed more than 100 thyroidectomies a year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies a year had 4 times as many complications.[211]

Radioactive Iodine

Postoperative Radioiodine

The NCCN Panel recommends a selective use approach to postoperative RAI remnant ablation. The 3 general, but overlapping, functions of postoperative RAI administration include: 1) ablation of the normal thyroid remnant, which may help in surveillance for recurrent disease (see below); 2) adjuvant therapy to try to eliminate suspected micrometastases; or 3) RAI therapy to treat known persistent disease. Postoperative RAI is recommended for patients at high risk of having persistent disease remaining after total thyroidectomy and includes patients with gross extrathyroidal extension, a primary tumor greater than 4 cm, or known/suspected distant metastases (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma). Postoperative RAI is also recommended for select patients who are at greater risk for recurrence based on clinical indications such as poorly differentiated histology, vascular invasion, clinically significant cervical lymph node metastases, and inappropriately elevated postoperative serum Tg.[3,212,213] However, the NCCN Panel does not routinely recommend RAI for patients with either unifocal or multifocal papillary microcarcinomas (<1 cm) confined to the thyroid. Guidelines from the ATA list very similar indications for postoperative RAI use and also provide specific guidance regarding the safe use of RAI in the outpatient setting.[3,214]

Studies show decreased recurrence and disease-specific mortality for populations at higher risk when postoperative 131I therapy is administered as part of the initial treatment.[19,113,121,215,216] In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was about 3-fold higher in patients either treated with thyroid hormone alone or given no postoperative medical therapy when compared with patients who underwent postoperative thyroid remnant ablation with 131I ($P < .001$). Moreover, fewer patients developed distant metastases ($P < .002$) after thyroid remnant 131I ablation than after other forms of postoperative treatment. However, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter.[215] Some found that remnant ablation had less of a therapeutic effect, perhaps because more extensive locoregional surgery had been done.[160]

Previously, it was reported that postoperative RAI was associated with decreased overall survival in patients with stage I thyroid cancer, although the deaths seemed unrelated to thyroid cancer.[217] Longer follow-up suggests that overall survival is not decreased or increased in these patients.[218] However, a recent study reported that the incidence of secondary malignancies, such as leukemia and salivary gland malignancies, has increased in patients with low-risk thyroid cancer (ie, T1N0) who received RAI.[219] Debate continues about ablating the thyroid bed with 131I after total thyroidectomy.[3,160,215,220] In patients with PTC who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates.[196,213] A recent long-term study (n=1298) found that overall survival is not improved in patients who receive RAI ablation.[221] Reasons favoring remnant ablation include: 1) simplified patient follow-up, because elimination of *thyroid bed* uptake prevents

misinterpretation of it as disease; 2) elimination of normal tissue as a source of Tg production, which facilitates identification of patients who are free of disease and may simplify their care while promoting early identification of those with residual cancer; and 3) elimination of normal tissue may eliminate the nidus for continued confounding anti-Tg antibody production. Conversely, others argue that most recurrences can be easily detected with neck ultrasound and that serum Tg levels are often quite low after a total thyroidectomy. Therefore, in patients at low and intermediate risk, the clinical benefit of routine remnant ablation as a requirement for optimal follow-up remains uncertain.

Recent data suggest that lower doses of RAI are as effective as higher doses—30 versus 100 mCi—for ablation in patients with low-risk thyroid cancer (eg, T1b/T2 [1-4 cm], clinical N0 disease).[30,31] The NCCN Guidelines reflect a more cautious approach to using RAI ablation based on these randomized trials.[222] If RAI ablation is used, the NCCN Guidelines recommend (category 1) 30 mCi of 131I for RAI ablation in patients at low risk based on these randomized trials. This same ablation dose—30 mCi—may be considered (category 2B) in patients at slightly higher risk (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).[223] RAI ablation is not recommended in patients at very low risk.

Diagnostic Total Body Imaging and Thyroid Stunning

When indicated, diagnostic total body 131I imaging is recommended by many (>50%), but not all (<85%), of the NCCN Panel (category 2B) after surgery to assess the completeness of thyroidectomy and to assess whether residual disease is present (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma). However, a phenomenon termed *stunning* may occur when imaging doses of 131I induce follicular cell damage.[224] Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent 131I.[225]

To avoid or reduce the stunning effect, the following have been suggested: 1) the use of 123I or small (2 or 3 mCi) doses of 131I; and/or 2) a shortened interval (≤72 hours) between the diagnostic 131I dose and the therapy dose. However, 123I is more expensive and smaller 131I doses have reduced sensitivity when compared with larger 131I doses.[224-226] In addition, a large thyroid remnant may obscure detection of residual disease with 131I imaging. Some experts recommend that diagnostic 131I imaging be avoided completely with decisions based on the combination of tumor stage and serum Tg.[224] Other experts advocate that whole-body 131I diagnostic imaging may alter therapy, for example: 1) when unsuspected metastases are identified; or 2) when an unexpectedly large remnant is identified that requires additional surgery or a reduction in RAI dosage to avoid substantial radiation thyroiditis.[3,224,227-229] Thus, NCCN Panel Members disagreed about using diagnostic total body 131I imaging before postoperative RAI, which is reflected in the category 2B recommendation for imaging.[3,230-232] Note that diagnostic imaging is used less often for patients at low risk.

Administration of Radioiodine Therapy

Historically, the 3 methods of determining 131I therapy activities (doses) have included: empiric fixed doses, quantitative dosimetry, and upper-bound limits that are set by blood dosimetry.[3,224,227,233,234] Most patients at NCCN Member Institutions receive RAI therapy based on empiric fixed dosing; a few centers use a combination of blood dosimetry and quantitative lesional dosimetry. In the past, hospitalization was required to administer therapeutic doses of 131I greater than 30 mCi (1110 MBq). However, hospitalization is no longer

necessary in most states, because a change in federal regulations permits the use of much larger 131I doses in patients who are ambulatory.[233] 131I therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses.

Fixed 131I Doses

Administration of a fixed dose of 131I is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of 131I in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of 131I. Lymph node metastases may be treated with about 100 to 175 mCi (3700 to 6475 MBq) of 131I. Cancer growing through the thyroid capsule (and incompletely resected) is treated with 150 to 200 mCi (5550 to 7400 MBq). Patients with distant metastases are usually treated with 200 mCi (7400 MBq) of 131I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in the elderly and in those with impaired kidney function.[235,236] Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of 131I (which is very uncommon) are treated with 150 mCi of 131I (5550 MBq) or less to avoid lung injury, which may occur when more than 80 mCi remain in the whole body 48 hours after treatment. The administered activity of RAI therapy should be adjusted for pediatric patients.[3,237-239] A recent pilot study demonstrated that targeted therapy of the MAP kinase pathway with a MEK inhibitor (selumetinib) significantly increased the effectiveness of RAI therapy in patients who were previously RAI refractory.[240]

Post-Treatment 131I Imaging

When 131I therapy is given, whole-body 131I imaging should be performed several days later to document 131I uptake by the tumor. Post-treatment whole-body 131I imaging should be done, primarily because up to 25% of images show lesions that may be clinically important, which were not detected by the diagnostic imaging.[233] In a study of pre-treatment and post-treatment imaging, the 2 differed in 27% of the treatment cycles, but only 10% of the post-treatment imaging showed clinically significant new foci of metastatic disease.[241] Post-treatment imaging was most likely to reveal clinically important new information in patients younger than 45 years who had received 131I therapy in the past. Conversely, in older patients and patients who had not previously received 131I therapy, post-treatment imaging rarely yielded new information that altered the patient's prognosis.[241]

Assessment and Management After Initial Treatment

Serum Tg determinations, neck ultrasound, and whole-body 131I imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation.[242] In contrast, neither serum Tg nor whole-body 131I imaging is specific for thyroid carcinoma in patients who have not undergone thyroidectomy and remnant ablation. When initial ablative therapy has been completed, serum Tg should be measured periodically. Serum Tg can be measured while the patient is taking thyroxine, but the test is more sensitive when thyroxine has been stopped or when recombinant human TSH (rhTSH) is given to increase the serum TSH.[243,244]

Using current Tg assays, patients with measurable serum Tg levels during TSH suppression and those with stimulated Tg levels more than 2 ng/mL are likely to have residual/recurrent disease that may be localized in almost 50% promptly and in an additional 30% over the next 3 to 5 years.[245] About 6% of patients with detectable serum Tg levels (which are <2 ng/mL after stimulation) will have recurrences over the next 3 to 5 years, whereas only about 2% of patients with completely undetectable serum Tg after stimulation will have recurrences over the

next 3 to 5 years. The long-term clinical significance is uncertain for disease only detected by minimally elevated Tg levels after stimulation.

Recombinant Human TSH

During follow-up, periodic withdrawal of thyroid hormone therapy has traditionally been used to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements with (or without) 131I imaging could be performed to detect residual thyroid tissue or carcinoma. However, patients dislike thyroid hormone withdrawal, because it causes symptomatic hypothyroidism. An alternative to thyroid hormone withdrawal is the administration of rhTSH intramuscularly, which stimulates thyroidal 131I uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.[246] rhTSH is well tolerated. Nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[244] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[246]

An international study was performed to assess the effects of 2 rhTSH dosing schedules on whole-body 131I imaging and serum Tg levels when compared with imaging and Tg levels obtained after thyroid hormone withdrawal.[244] Data showed that the combination of rhTSH–stimulated whole-body imaging and serum Tg measurements detected 100% of metastatic carcinoma.[244] In this study, 0.9 mg of rhTSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of 131I on the third day. Whole-body imaging and Tg measurements were performed on the fifth day. Whole-body 131I images were acquired after 30 minutes of imaging or after obtaining 140,000 counts, whichever came first. A serum Tg of 2.0 ng/mL or higher, obtained 72 hours after the last rhTSH injection, indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole-body imaging findings.[244,247]

Measuring Serum Tg

Serum Tg measurement is the best means of detecting thyroid tissue, including carcinoma. Tg should be measured when TSH has been stimulated—either by thyroid hormone withdrawal or by rhTSH—because in this setting, serum Tg has a lower false-negative rate than whole-body 131I imaging.[243-245,248] Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or rhTSH stimulation. Serum Tg generally does not rise as high after rhTSH administration as after withdrawal of thyroid hormone. The conditions for rhTSH–stimulated, whole-body 131I imaging stipulate using 4-mCi 131I doses (based on the trial)[244] and an imaging time of 30 minutes or until 140,000 counts are obtained.

The sensitivity and specificity of various Tg assays, however, vary widely in different laboratories, even with the use of an international standard (CRM 457).[249,250] Thus, it is recommended that patients undergo Tg monitoring via the same Tg assay performed in the same laboratory. Ideally, serum is frozen and saved for future analyses if needed, especially should a change in Tg assay be necessary. As the sensitivity of commercially available Tg assays improves, the need for stimulated Tg testing is likely to become less important.

Anti-Tg antibodies should be measured in the same serum sample taken for Tg assay, because these antibodies (which are found in ≤25% of patients with thyroid carcinoma) invalidate serum Tg measurements in most assays.[250,251] These antibodies typically falsely lower the Tg value in immunochemiluminometric assays (ICMAs) and immunoradiometric assays (IRMA), while raising the value in older RAIs. Although the clinical importance of anti-Tg antibodies is unclear,

their persistence for more than 1 year after thyroidectomy and RAI ablation probably indicates the presence of residual thyroid tissue and possibly an increased risk of recurrence.[251]

In one study, 49% of patients had a recurrence if they had undetectable serum Tg and serum anti-Tg antibody levels of 100 U/mL or more when compared with only 3% of patients with undetectable serum Tg and serum anti-Tg antibodies of less than 100 U/mL.[252] In patients with coexistent autoimmune thyroid disease at the time of surgery, anti-Tg antibodies may persist far longer. In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for up to 20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.[253]

Treating Patients With Positive Tg and Negative Imaging

Post-treatment 131I imaging may indicate the location of metastases when the serum Tg level is increased, but a tumor [or metastases] cannot be found by physical examination or other localizing techniques such as diagnostic 131I imaging, neck ultrasonography, CT, MRI, or PET. Pulmonary metastases may be found only after administering therapeutic doses of 131I and obtaining whole-body imaging within a few days of treatment.[254] In a study of 283 patients treated with 100 mCi (3700 MBq) of 131I, 6.4% had lung and bone metastases detected after treatment that had been suspected based on high serum Tg concentrations alone but had not been detected after 2-mCi (74 MBq) diagnostic imaging.[255]

Unfortunately, most patients who are diagnostic imaging–negative and Tg-positive are not rendered disease free by 131I therapy; however, the tumor burden may be diminished.[256] Thus, most patients with residual or recurrent disease confined to the neck undergo re-operation rather than RAI therapy in the hopes of a cure. RAI therapy is more commonly considered for those with distant metastases or inoperable local disease. Patients not benefiting from this therapy can be considered for clinical trials, especially those patients with progressive metastatic disease. When a large tumor is not visible on diagnostic whole-body imaging, its ability to concentrate 131I is very low; thus, the tumor will not respond to 131I therapy.

Thyroid Hormone Suppression of TSH

The use of levothyroxine to decrease TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma, because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium.[3,227,257] However, the optimal serum levels of TSH have not been defined because of a lack of specific data; therefore, the NCCN Panel recommends tailoring the degree of TSH suppression to the risk of recurrence and death from thyroid cancer for each individual patient. For patients with known residual carcinoma (or those at high risk for recurrence), the recommended TSH level is below 0.1 mU/L. For patients at low risk and for those patients with an excellent response to initial therapy who are in remission, the recommended TSH level is either slightly below or slightly above the reference range. The risk and benefit of TSH-suppressive therapy must be balanced for each individual patient because of the potential toxicities associated with TSH-suppressive doses of levothyroxine, including cardiac tachyarrhythmias (especially in the elderly), bone demineralization (particularly in post-menopausal women), and frank symptoms of thyrotoxicosis.[3,258] An adequate daily intake of calcium (1200 mg/day) and vitamin D (1000 units/day) is recommended for patients whose TSH levels are chronically suppressed.

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated

with thyroid hormone suppressive therapy.[19,215,217,257,259-261] The average dosage needed to attain serum TSH levels in the euthyroid range is higher in patients who have been treated for thyroid carcinoma (2.11 mcg/kg per day) than in those patients with spontaneously occurring primary hypothyroidism (1.62 mcg/kg per day).[261] Even higher doses are required to suppress serum TSH in patients who have been treated for thyroid carcinoma. The optimal TSH level to be achieved is uncertain in patients who have been treated for thyroid carcinoma. Superior outcomes were associated with aggressive thyroid hormone suppression therapy in patients at high risk but were achieved with modest suppression in patients with stage II disease.[217] Excessive TSH suppression (into the undetectable, thyrotoxic range) is not required to prevent disease progression in all patients who have been treated for differentiated thyroid carcinoma.

Adjuvant External-Beam RT

No prospective controlled trials have been completed using adjuvant external-beam radiation therapy (EBRT).[262] One retrospective study reported a benefit of adjuvant EBRT after RAI in patients older than 40 years with invasive PTC (T4) and lymph node involvement (N1).[263] Local recurrence and locoregional and distant failure were significantly decreased. A second study reported increased cause-specific survival and local relapse-free rate in select patients treated with adjuvant EBRT (in addition to total thyroidectomy and TSH-suppressive therapy with thyroid hormone) for PTC with microscopic residuum. Not all patients received RAI therapy.[113] Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of PTC. Similarly, patients with microscopic residual papillary carcinoma after surgery are more commonly rendered disease free after receiving EBRT (90%) than those who do not receive it (26%).[264] In another study, patients with microscopically invasive follicular thyroid carcinoma after surgery were also more often disease free when postoperative EBRT was given (53%) than when it was not given (38%).[264] However, these patients had not received RAI. Similar benefit was shown with RAI alone in comparable patients treated with RAI after surgery.[264] Another study found that recurrences did not occur in patients at high risk who received EBRT, but recurrences did occur in those who did not receive EBRT. However, the study was not powered to detect a statistical significance.[265]

External-Beam RT and Surgical Excision of Metastases

Surgical excision or external irradiation should be considered for isolated skeletal metastases. Brain metastases pose a special problem, because 131I therapy may induce cerebral edema. Neurosurgical resection can be considered for brain metastases. For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery is preferred over whole brain radiation.[266,267] Once brain metastases are diagnosed, disease-specific mortality is very high (67%), with a reported median survival of 12.4 months in one retrospective study. Survival was significantly improved by surgical resection of one or more tumor foci.[268] Most recurrent tumors respond well to surgery, 131I therapy, or EBRT.[3,269]

Systemic Therapy

Systemic therapy can be considered for tumors that are not surgically resectable, are not responsive to 131I, are not amenable to EBRT treatment, and have clinically significant structural disease progression during the last 6 to 12 months. Among 49 patients with metastatic differentiated thyroid carcinoma who were treated with 5 chemotherapy protocols, only 2 (3%) patients had objective responses.[270] In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.[271] Combination chemotherapy is not clearly superior to doxorubicin therapy alone.[114] Overall, traditional

cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease.[272]

Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.[273-278] Agents include multitargeted kinase inhibitors, such as sorafenib,[279-286] sunitinib,[284,287] axitinib,[288,289] vandetanib,[290] pazopanib,[291] and lenvatinib;[274,292-295] and BRAF (V600E) mutation inhibitors, such as vemurafenib.[296]

Clinical trials suggest that kinase inhibitors have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of subjects, usually for about 12 to 24 months.[274,284,291,297-299] Vandetanib and cabozantinib, oral kinase inhibitors, are recommended for the treatment of MTC in patients with unresectable locally advanced or metastatic disease (see *Medullary Thyroid Carcinoma* in this Discussion and the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[300-303] Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, stroke, and liver toxicity; however, most side effects can be managed and are reversible with discontinuation of the drug.[304] Pazopanib has been reported to cause reversible hypopigmentation.[305]

Papillary Thyroid Carcinoma

Surgical Therapy

Imaging is performed before surgery to ascertain the extent of disease and to aid in the surgical decision-making process. A cervical ultrasound, including the thyroid and the central & lateral compartments, is the principal imaging modality that is recommended.[306] In one report, cervical ultrasound performed before primary surgery for newly diagnosed thyroid cancer identified metastatic sites not appreciated on physical examination in 20% of patients, and surgical strategy was altered in 39% of patients.[307] At the University of Miami, surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients.[308] In a study of more than 700 patients with PTC from the Mayo Clinic, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects.[309] Preoperative ultrasound findings altered the operation in more than 40% of cases. In a report from the Medical College of Wisconsin,[310] operative management was altered in 23% of the total group due to findings on the preoperative ultrasound. These studies indicate that preoperative ultrasound has a high sensitivity for nodal disease and will detect nonpalpable nodal metastases in 20% to 33% of patients, and ultrasound should alter the index operation in a similar percentage of patients. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases. Cross-sectional imaging (CT or MRI) should be performed if the thyroid lesion is fixed, bulky, or substernal. Iodinated contrast is required for optimal cervical imaging with CT. Evaluation of vocal cord mobility can be considered. A chest x-ray can also be considered.

The NCCN Panel agreed on the characteristics of patients at higher risk who require total thyroidectomy and neck dissection as the primary treatment (see *Preoperative or Intraoperative Decision-Making Criteria* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,311,312] A total thyroidectomy is recommended for patients with any one of the following factors, including: radiation history, known distant metastases, bilateral nodularity, extrathyroidal extension, tumor greater than 4 cm in diameter, cervical lymph node metastases, or poorly differentiated histology. Clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level VI dissection.

In the lateral compartment, a formal modified radical neck dissection including levels II, III, IV, and Vb should be performed.[313] Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. If the cervical lymph nodes are clinically negative, prophylactic central neck dissection (level VI) can be considered (category 2B) but is not required.[314-318] Prophylactic modified radical neck dissection is not recommended for differentiated thyroid cancer of follicular cell origin. Central neck dissection will be required ipsilateral to a modified radical neck dissection done for clinically involved lateral neck lymph nodes in most cases. Selective dissection of individual nodal metastases (ie, cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field.

The NCCN Panel did not uniformly agree about the preferred primary surgery for patients who are assumed to be at lower risk of cancer-specific mortality. The majority of panel members recommended (category 2B) total thyroidectomy in any patient in whom PTC was identified preoperatively or at the time of surgery. However, a minority of panel members recommended (category 2B) that, initially, lobectomy plus isthmusectomy is adequate surgery for properly selected patients at low risk of recurrence. Lobectomy plus isthmusectomy is recommended for patients who cannot (or refuse to) take thyroid hormone replacement therapy for the remainder of their lives.[319] Note that some patients prefer to have total thyroidectomy to avoid having a second surgery (ie, completion thyroidectomy). Other patients prefer to have a lobectomy in an attempt to avoid thyroid hormone replacement.

A study of more than 5000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for patients at low and high risk.[320] An observational study (SEER database) in more than 35,000 patients with PTC limited to the thyroid gland suggests that survival is similar whether (or not) patients are treated in the first year after diagnosis and whether they undergo lobectomy or total thyroidectomy.[321] However, most guidelines (eg, NCCN, ATA) do not recommend observation for patients with PTC.[3] Another study in 2784 patients with differentiated thyroid carcinoma (86% with PTC) found that total thyroidectomy was associated with increased survival in patients at high risk.[217] A study in 52,173 patients found that total thyroidectomy reduces recurrence rates and improves survival in patients with PTC of 1 cm or more when compared with lobectomy.[322] For patients at lower risk who undergo lobectomy plus isthmusectomy, completion of thyroidectomy is recommended for any one of the following risk factors: large tumor (>4 cm), positive margins, gross extrathyroidal extension, macroscopic multifocal disease, vascular invasion, or macroscopic nodal metastases.

Incidentally discovered PTCs 1 to 4 cm in size may warrant a completion thyroidectomy (category 2B) for lymphovascular invasion (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma); observation (category 2B) is another option for these patients (ie, with measurement of Tg and anti-Tg antibodies). Levothyroxine therapy can be considered for these patients to maintain the TSH levels at low or normal (see *Principles of TSH Suppression* in the NCCN Guidelines for Thyroid Carcinoma). Lobectomy is sufficient for tumors resected with all of the following: negative margins, no contralateral lesion, no suspicious lymph node(s), and small (<1 cm) PTCs found incidentally on the final pathology sections; these patients are observed (ie, with measurement of Tg and anti-Tg antibodies). Levothyroxine therapy to reduce serum TSH to low or low-normal concentrations can be considered for these patients (see *Principles of TSH Suppression* in the NCCN Guidelines for Thyroid Carcinoma).

Radioactive Iodine

For the 2014 update, a list of clinicopathologic factors that can be used to guide decisions about whether to use initial postoperative RAI was added to the algorithm (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 1 to 4 cm, but the final decision depends on the combination of individual clinical factors as outlined in the algorithm. New algorithms have been added to assist in decision making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease.

Therapy with 131I is typically recommended for patients with 1) gross extrathyroidal extension; 2) primary tumor greater than 4 cm; or 3) postoperative unstimulated Tg greater than 5 to 10 ng/mL. All patients should be examined, and palpable neck disease should be surgically resected before any RAI treatment. A negative pregnancy test is required before the administration of RAI in women of child-bearing potential. The administered activity of RAI therapy should be adjusted for pediatric patients.[239] RAI is not typically recommended for patients with either unifocal or multifocal papillary microcarcinomas (<1 cm) confined to the thyroid, and clinical N0 and M0.[222] The NCCN Panel agrees that RAI treatment is not needed for patients with Tg levels less than 1 ng/mL, negative 131I imaging, no concerning findings on ultrasound, and negative anti-Tg antibodies. RAI is selectively recommended if any of the following are present: 1) primary tumor 1 to 4 cm; 2) poorly differentiated histology; 3) lymphovascular invasion; 4) cervical lymph node metastases; 5) macroscopic multifocality (ie, one focus >1 cm); 6) anti-Tg antibodies; or 7) postoperative unstimulated Tg less than 5 to 10 ng/mL. For patients with suspected or proven RAI-responsive residual tumor, RAI treatment is recommended (100–200 mCi) followed by post-treatment imaging; dosimetry can be considered for distant metastases (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3]

For unresectable locoregional recurrence, RAI treatment and EBRT are recommended if the 131I imaging is positive; EBRT alone is another option in the absence of 131I uptake.[323,324] When recurrent disease is suspected based on high serum-stimulated Tg values (>10 ng/mL) and negative imaging studies (including PET scans), RAI therapy can be considered (category 3) using an empiric fixed dose of 100 to 150 mCi of 131I (see *Recurrent Disease* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). However, the NCCN Panel had a major disagreement about this recommendation (category 3), because some do not feel that these patients should receive RAI. No study has shown a decrease in morbidity or mortality in patients treated with 131I on the basis of increased Tg measurements alone. In a long-term follow-up study, no survival advantage was associated with empiric high-dose RAI in patients with negative imaging.[325] Further, potential long-term side effects (ie, xerostomia, nasolacrimal duct stenosis, bone marrow and gonadal compromise, the risk of hematologic and other malignancies) may negate any benefit.[326,327]

For patients with metastatic disease, the NCCN Panel recommends individualized treatment based on the tumor location(s) (eg, CNS, bone, soft tissue) (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Sorafenib may be considered for progressive and/or symptomatic disease based on a recent phase 3 randomized trial.[279] Other

commercially available small molecule kinase inhibitors may also be considered for progressive and/or symptomatic disease—including axitinib, pazopanib, sunitinib, or vandetanib—although none have been approved by the FDA for differentiated thyroid cancer (see *Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer* in the NCCN Guidelines for Thyroid Carcinoma).[328] Note that kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease, because it may cause severe side effects.[329,330] Watchful waiting may be appropriate for asymptomatic patients with indolent disease.

Adjuvant External-Beam RT

For patients with unresectable gross residual disease in the neck (suspected or proven) that does not concentrate RAI, EBRT is recommended (see *Postsurgical Evaluation* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,323,331-334]

Surveillance and Maintenance

The recommendations for surveillance and maintenance are described in the algorithm (see *Surveillance and Maintenance* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3] In patients who have had total (or near total) thyroidectomy and thyroid remnant ablation, the ATA Guidelines define the absence of persistent tumor (ie, disease free) as: 1) absence of clinical evidence of tumor; 2) absence of imaging evidence of tumor; and 3) undetectable Tg levels (during TSH suppression) and absence of anti-Tg antibodies.[3] Patients treated with 131I ablation may be followed with unstimulated Tg annually and with periodic neck ultrasound if they have negative ultrasounds, stimulated Tg less than 2 ng/mL (with negative anti-Tg antibodies), and negative RAI imaging (if performed). However, if they have a clinical suggestion of recurrent disease, then TSH-stimulated testing (or other imaging) may be considered. A subgroup of patients at low risk (eg, micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic neck ultrasound follow-up (without stimulated Tg or follow-up whole-body imaging) as long as their basal Tg remains low (see *Surveillance and Maintenance* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.[3]

Recurrent and Metastatic Disease

The NCCN Panel agrees that surgery is the preferred therapy for locoregional recurrent disease if the tumor is resectable (see *Recurrent Disease* in the NCCN Papillary [Thyroid] Carcinoma algorithm). Cervical ultrasound, including the central and lateral compartments, is the principal imaging modality when locoregional recurrence is suspected. Cross-sectional imaging with CT or MRI may also be valuable, especially when reliable high-resolution diagnostic ultrasound is unavailable and/or there is suspicion of invasion into the aerodigestive tract. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases.

Clinically significant nodal recurrence in a previously undissected nodal basin should be treated with a formal compartmental resection. In the central neck, this is usually achieved through a unilateral level VI dissection and, occasionally, a level VII dissection. In the lateral compartment, a formal modified radical neck dissection—including levels II, III, IV, and Vb—should be performed. Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Selective dissection of individual nodal metastases

(cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field, and is not recommended in the NCCN Thyroid Carcinoma algorithm. Clinically significant nodal recurrence detected in a previously dissected nodal basin may be treated with a more focused dissection of the region containing the metastatic disease. For example, a level II recurrence detected in a patient who underwent a modified radical neck dissection as part of the primary treatment may only require selective dissection of level II. Likewise, a central neck recurrence detected in a patient who underwent a central neck dissection as part of the primary treatment may only require a focused resection of the region of recurrence.

For unresectable locoregional recurrences, 131I therapy is recommended for tumors that concentrate 131I (ie, 131I imaging positive), and EBRT alone is recommended for those that do not concentrate 131I (ie, 131I imaging negative). Unresectable iodine-responsive locoregional disease may additionally be treated with EBRT to improve outcomes. For metastatic disease, several therapeutic approaches are recommended (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma), depending on the site and number of tumor foci.[3,335] Patients should continue to receive levothyroxine to suppress TSH levels. For skeletal metastases, consider surgical palliation for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are 131I treatment (if the 131I imaging is positive) and/or EBRT.[336-338] Intravenous bisphosphonate (eg, pamidronate or zoledronic acid) or denosumab therapy may be considered for bone metastases; data show that these agents prevent skeletal-related events.[339-341] Embolization of metastases can also be considered either prior to resection or as an alternative to resection.[336,342]

For metastases to the CNS, neurosurgical resection should be considered for appropriate cases and/or image-guided EBRT (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred (see the NCCN Guidelines for Central Nervous System Cancers).[266,267] For sites other than the CNS, surgical resection and/or EBRT can be considered for progressive or symptomatic metastases; 131I is recommended if the tumor concentrates the radioisotope. For clinically progressive or symptomatic disease, recommended options include: 1) clinical trials for non-131I–responsive tumors; 2) consider small molecule kinase inhibitors or systemic therapy if a clinical trial is not available; or 3) sorafenib.[328,343] Because chemotherapy is usually not effective, the NCCN Guidelines recommend clinical trials for non-RAI avid tumors; small molecule kinase inhibitors (ie, axitinib, sunitinib, pazopanib, vandetanib) or traditional cytotoxic systemic therapy can be considered if a trial is not available.[3,280,282,285,286,288,291,344-346] However, kinase inhibitor therapy may be most appropriate for patients with unresectable recurrent disease that is threatening vital structures or is not responsive to EBRT.[347] Of interest, hypothyroidism has been reported in some patients receiving sunitinib or sorafenib, but it also seems to be associated with increased progression-free survival (PFS).[330,348]

Follicular Thyroid Carcinoma

Because the diagnosis and treatment of papillary and follicular thyroid carcinoma are similar, only the important differences in the management of follicular carcinoma are highlighted. The diagnosis of follicular thyroid carcinoma requires evidence of invasion through the capsule of the nodule or the presence of vascular invasion.[43,349] Thus, FNA is not specific for follicular thyroid carcinoma (unlike papillary

carcinoma) and accounts for the main differences in management of the 2 tumor types.[67,73,100,350] The FNA cytologic diagnosis of [*suspicious for*] *follicular neoplasm* will prove to be a benign follicular adenoma in 80% of cases. However, 20% of patients with follicular neoplasms on FNA are ultimately diagnosed with follicular thyroid carcinoma when the final pathology is assessed. Further diagnostic and treatment decisions for patients who present with follicular neoplasms are based on their TSH levels (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Because most patients with follicular neoplasms on FNA actually have benign disease, total thyroidectomy is recommended only if invasive cancer or metastatic disease is apparent at the time of surgery or if the patient opts for total thyroidectomy to avoid a second procedure (ie, completion thyroidectomy) if cancer is found at pathologic review.[349,351] Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery. If invasive follicular thyroid carcinoma (extensive vascular invasion) is found on the final histologic sections after lobectomy plus isthmusectomy, prompt completion of thyroidectomy is recommended (see *Primary Treatment* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

Completion thyroidectomy is also recommended for tumors that, on final histologic sections after lobectomy plus isthmusectomy, are identified as minimally invasive follicular thyroid carcinomas. *Minimally invasive* cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections.[352] These tumors may also be simply followed carefully, because minimally invasive follicular carcinomas usually have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma do occasionally occur. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see *Recurrent Disease* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

The other features of management and follow-up for follicular thyroid carcinoma are similar to those of papillary carcinoma. For the 2014 update, a list of clinicopathologic factors that can be used to guide decisions about whether to use initial postoperative RAI was added to the algorithm (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 2 to 4 cm, but the final decision depends on the combination of individual clinical factors as outlined in the algorithm. New algorithms have been added to assist in decision making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease.

RAI ablation to destroy residual thyroid tissue is recommended for suspected or proven thyroid bed uptake. 131I ablation and post-treatment imaging (with consideration of dosimetry for distant metastasis) is recommended for suspected or proven 131I-avid metastatic foci (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). The decision to perform diagnostic whole-body 131I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before 131I therapy is administered is a category 2B recommendation for both follicular and PTC because of the problem of stunning (see section on *Diagnostic Total Body Imaging and Thyroid Stunning* in this Discussion).

Hürthle Cell Carcinoma

This tumor (also known as oxyphilic cell carcinoma) is usually assumed to be a variant of follicular thyroid carcinoma,[146,147] although the prognosis of Hürthle cell carcinoma is worse.[152,349,351,353,354] The Hürthle cell variant of PTC is rare and seems to have a prognosis similar to follicular carcinoma.[355] The management of Hürthle cell (oxyphilic) carcinoma is almost identical to follicular thyroid carcinoma, except that 1) locoregional nodal metastases may be more common, and therefore therapeutic lymph node dissections of the affected compartment may be needed for clinically apparent biopsy proven disease; and 2) metastatic Hürthle cell tumors are less likely to concentrate 131I. Postoperative EBRT can be considered for 1) unresectable primary Hürthle cell lesions that do not concentrate 131I; and 2) unresectable locoregional recurrence (see *Postsurgical Evaluation* and *Recurrent Disease* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma), similar to the management for papillary carcinoma.[3]

For the 2014 update, a list of clinicopathologic factors that can be used to guide decisions about whether to use initial postoperative RAI was added to the algorithm (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 2 to 4 cm, but the final decision about whether to use RAI depends on the combination of individual clinical factors as outlined in the algorithm. New algorithms have been added to assist in decision making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease.

RAI therapy has been reported to decrease the risk of locoregional recurrence and is recommended for unresectable disease with positive 131I imaging. 131I therapy (100–150 mCi) may be considered (category 3) after thyroidectomy for patients with stimulated Tg levels of more than 10 ng/mL who have negative scans (including FDG-PET) (see *Recurrent Disease* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma).[152]

NCCN Panel Members do not all agree about the following recommendations, which are reflected in the category 2B decisions. Some NCCN Panel Members do not feel that diagnostic total body 131I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) should be recommended (category 2B) before 131I therapy is administered, because the thyroid remnant may interfere with the scan.[3] Other panel members do not feel that patients with clinical indications for RAI (suspicion based on pathology, postoperative Tg, and intraoperative findings) require imaging (category 2B) (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma).

Medullary Thyroid Carcinoma

MTC arises from the neuroendocrine parafollicular C cells of the thyroid.[356-358] Sporadic MTC accounts for about 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as: 1) MEN type 2A (MEN 2A), which is the most common type; 2) MEN 2B; or 3) familial MTC.[359,360] Sporadic disease typically presents in the fifth or sixth decade of life. Familial forms of the disease tend to present at earlier ages.[356] The 10-year overall survival is about 75%.[15] Because the C cells are predominantly located in the upper portion of each thyroid lobe, patients with sporadic disease typically present with upper pole nodules. Metastatic cervical adenopathy appears in about

50% of patients at initial presentation. Symptoms of upper aerodigestive tract compression or invasion are reported by up to 15% of patients with sporadic disease.[361] Distant metastases in the lungs or bones cause symptoms in 5% to 10% of patients. Many patients with advanced MTC can have diarrhea, Cushing's syndrome, or facial flushing, because the tumor can secrete calcitonin and sometimes other hormonally active peptides (ie, adrenocorticotropic hormone [ACTH], calcitonin gene-related peptide [CGRP]). Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms.[362] However, patients with unresectable or metastatic disease may have either slowly progressive or rapidly progressive disease.

Nodule Evaluation and Diagnosis

Patients with MTC can be identified by using pathologic diagnosis or by prospective genetic screening. Separate pathways are included in the algorithm (see *Clinical Presentation* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma) depending on the method of identification.

Sporadic MTC

Sporadic MTC is usually suspected after FNA of a solitary nodule (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). Reports suggest that about 3% of patients with nodular thyroid disease will have an increased serum calcitonin level when measured by a sensitive immunometric assay; 40% of these patients will have MTC at thyroidectomy.[363-365] However, routine measurement of the basal serum calcitonin concentration is not recommended by the NCCN Panel for evaluating a patient with nodular thyroid disease because of the expense of screening all thyroid nodules and only finding a few cases of MTC, the lack of confirmatory pentagastrin stimulation testing, and the resulting need for thyroidectomy in some patients who actually have benign thyroid disease.[366,367] The ATA is equivocal about routine calcitonin measurement.[3]

Inherited MTC

For patients in known kindreds with inherited MTC, prospective family screening with testing for mutant ret genes can identify disease carriers long before clinical symptoms or signs are noted.[357,358] The traditional approach of stimulating secretion of calcitonin by either pentagastrin or calcium infusion to identify patients with MTC is no longer recommended, because elevated calcitonin is not a specific or adequately sensitive marker for MTC[368] and because pentagastrin is no longer available in the United States. When MEN 2A is suspected, the NCCN Guidelines recommend measurement of calcium levels with (or without) serum intact parathyroid hormone levels (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade of life, without gender preference. In patients with MEN 2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.

All familial forms of MTC and MEN 2 are inherited in an autosomal-dominant fashion. Mutations in the *RET* proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of familial MTC.[357,358,369] Familial MTC is now viewed as a variant of MEN 2A.[356] The *RET* proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN 2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; MEN 2B and some familial MTC mutations are found within the intracellular exons 14 to 16.[356] Somatic mutations in exons 11, 13, and 16 have also been found in at least 25%

of sporadic MTC tumors—particularly the codon 918 mutation that activates the tyrosine kinase function of the receptor—and is associated with poorer prognosis of the patient.

About 6% of patients with clinically sporadic MTC carry a germline mutation in *RET*, leading to identification of new kindreds with multiple (previously undiagnosed) affected individuals.[370,371] Genetic testing for *RET* proto-oncogene mutations is recommended for all newly diagnosed patients with clinically apparent sporadic MTC, and for screening children and adults in known kindreds with inherited forms of MTC;[372] genetic counseling should be considered. MTC can involve difficult ethical decisions for clinicians if parents or guardians refuse screening and/or treatment for children with possible MTC.[373]

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum carcinoembryonic antigen [CEA]) and screening patients with germline *RET* proto-oncogene mutations for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A). Before surgery for MTC, it is important to diagnose and address coexisting pheochromocytoma to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine Tumors). Pheochromocytoma can be removed using laparoscopic adrenalectomy.[356,374] Preoperative thyroid and neck ultrasound (including central and lateral neck compartments) is recommended. Contrast-enhanced CT or MRI of the chest and mediastinum can be considered if the patient has N1 disease or calcitonin greater than 400 pg/mL.[356] Evaluation of vocal cord mobility can also be considered.

Staging

As previously mentioned, the NCCN Guidelines for Thyroid Carcinoma do not use TNM stages to guide therapy. Instead, many characteristics of the tumor and patient play important roles in these NCCN Guidelines. Many specialists in thyroid cancer also follow this paradigm. The TNM criteria for clinicopathologic tumor staging are based on tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (see Table 1) (7th edition of the AJCC Cancer Staging Manual).[146] Staging for MTC slightly changed in the 2010 AJCC update (ie, 7th edition of the AJCC Cancer Staging Manual).[146] In the 7th edition, T3,N0,M0 has been downstaged from stage III to stage II. All follow-up studies (in this Discussion) reporting on AJCC-TNM staging have referred to the 5th edition[175] and not to the 6th or 7th editions.[146,174] In one study with a median follow-up period of only 4 years, mortality from MTC was 0% for stage I, 13% for stage II, 56% for stage III, and 100% for stage IV disease.[375]

However, the TNM staging classification lacks other important prognostic factors.[376] Notably absent is the age at diagnosis. Patients younger than 40 years at diagnosis have a 5- and 10-year disease-specific survival rate of about 95% and 75%, respectively, compared with 65% and 50% for those older than 40 years.[361,376] Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically are diagnosed at an earlier age) is probably similar to those with sporadic disease.[377,378] Despite an even younger typical age at diagnosis, however, patients with MEN 2B who have MTC are more likely than those with MEN 2A (or familial MTC) to have locally aggressive disease.[378]

Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining

of the tumor;[379] 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level;[380] and 3) postoperative residual hypercalcitoninemia.[375] A study comparing different staging systems found that a system incorporating age, gender, and distant metastases (EORTC) had the greatest predictive value; however, the AJCC staging system was deemed to be the most appropriate.[376,381] Codon analysis is useful for predicting prognosis.[356,382] Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease.[383] More than 95% of patients with MEN 2B have a mutation in exon 16 (codon 918), whereas 2% to 3% have a mutation in exon 15 (codon 883).[384]

Surgical Management

Surgery is the main treatment for MTC, because no curative systemic therapy for MTC is available, although vandetanib and cabozantinib are recommended for locally advanced and metastatic MTC (see *Recurrent or Persistent Disease* in this Discussion).[300-303] MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, 131I imaging cannot be used, and RAI treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, TSH suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levothyroxine dose.[356]

Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease, because the possibility of MEN 2 should dictate testing for a *RET* proto-oncogene mutation for all patients with MTC. Pheochromocytomas should be removed (eg, laparoscopic adrenalectomy) before surgery on the thyroid to avoid hypertensive crisis during surgery. Patients with pheochromocytomas must be treated preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery. Forced hydration and alpha-blockade are necessary to prevent hypotension after the tumor is removed. After institution of alpha-blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is 1 cm or larger or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is less than 1 cm and for unilateral thyroid disease (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[311,361] Given the risks of thyroidectomy in very young children, referral to a surgeon and team with experience in pediatric thyroid surgery is advised.

If a patient with inherited disease is diagnosed early enough, the recommendation is to perform a prophylactic total thyroidectomy by age 5 years or when the mutation is identified (in older patients), especially in patients with codon 609, 611, 618, 620, 630, or 634 *RET* mutations.[356,385] Note that C634 mutations are the most common mutation.[356] Total thyroidectomy is recommended in the first year of life or at diagnosis for MEN 2B patients with codon 883 *RET* mutations, 918 *RET* mutations, or compound heterozygous (V804M + E805K, V804M + Y806C, or V804M + S904C) *RET* mutations (see *Clinical Presentation* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma), because these *RET* mutations carry the highest risk for MTC (ie, level D).[356,386]

However, for patients with codon 768, 790, 791, 804, and 891 *RET* (risk level A) mutations, the lethality of MTC may be lower than with other *RET* mutations.[356,386] In patients with these less high-risk (ie, lower-risk level A) *RET* mutations, annual basal calcitonin testing and annual

ultrasound are recommended; total thyroidectomy and central node dissection may be deferred if these tests are normal, there is no family history of aggressive MTC, and the family agrees to defer surgery (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[356,387] Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.[356,388] A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with RET mutations for MEN 2A; longer follow-up is necessary to determine if these patients are cured.[389]

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.[356] A bilateral central neck dissection (level VI) can be considered for all patients with MEN 2B. For those patients with MEN 2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if patients have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for these patients with primary tumor(s) 1 cm or larger in diameter (>0.5 cm for patients with MEN 2B) or for patients with central compartment lymph node metastases (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

With a concurrent diagnosis of hyperparathyroidism in MEN 2A or familial MTC, the surgeon should leave or autotransplant the equivalent mass of one normal parathyroid gland if multiglandular hyperplasia is present. Cryopreservation of resected parathyroid tissue should be considered to allow future implantation in the event of iatrogenic hypoparathyroidism. Disfiguring radical node dissections do not improve prognosis and are not indicated. In the presence of grossly invasive disease, more extended procedures with resection of involved neck structures may be appropriate. Function-preserving approaches are preferred. In some patients, MTC is diagnosed after thyroid surgery. In these patients, additional workup is recommended to ascertain whether they have RET proto-oncogene mutations (eg, exons 10, 11, 13–16), which will determine whether they need additional surgery (eg, completion thyroidectomy and/or neck dissection); genetic counseling should be considered (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

Adjuvant RT

EBRT has not been adequately studied as adjuvant therapy in MTC.[390] Slight improvements in local disease-free survival have been reported after EBRT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement.[391] However, most centers do not have extensive experience with adjuvant EBRT for this disease. When EBRT is used, 40 Gy is typically administered in 20 fractions to the cervical, supraclavicular, and upper mediastinal lymph nodes over 4 weeks, with subsequent booster doses of 10 Gy in 5 fractions to the thyroid bed.[233] Postoperative adjuvant EBRT to the neck and mediastinum may be considered for patients with gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and after resection of moderate-volume to high-volume disease in the central or lateral neck lymph nodes with extranodal soft tissue extension; however, this is rarely recommended in children (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[356] EBRT can also be given to palliate painful or progressing bone metastases.[338,356]

Persistently Increased Calcitonin

Basal serum concentrations of calcitonin and CEA should be measured 2 or 3 months postoperatively. About 80% of patients with palpable MTC and 50% of those with nonpalpable but macroscopic MTC who undergo supposedly curative resection have serum calcitonin values indicative of residual disease. Those patients with residual disease may benefit from further evaluation to detect either residual resectable disease in the neck or the presence of distant metastases. Patients with detectable basal calcitonin or elevated CEA who have negative imaging and who are asymptomatic may be followed (see *Surveillance* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

Patients with a basal serum calcitonin value greater than 1000 pg/mL—and with no obvious MTC in the neck and upper mediastinum—probably have distant metastases, most likely in the liver. However, occasionally patients have relatively low serum CEA and calcitonin levels but have extensive metastatic disease; initial postoperative imaging is therefore reasonable despite the absence of very high serum markers.

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease, 15 patients with MEN 2A, and 6 patients with MEN 2B), the 5- and 10-year survival rates were 90% and 86%, respectively.[392] Two studies have reported higher mortality rates for patients with high postoperative serum calcitonin values, with more than 50% of patients having a recurrence during a mean follow-up of 10 years.[375,393] Routine lymphadenectomy or excision of palpable tumor generally fails to normalize the serum calcitonin concentrations in such patients; therefore, some have focused on detection and eradication of microscopic tumor deposits with a curative intent in patients without distant metastases. Extensive dissection to remove all nodal and perinodal tissue from the neck and upper mediastinum was first reported to normalize the serum calcitonin levels in 4 of 11 patients at least 2 years postoperatively.[394] In subsequent larger studies, 20% to 40% of patients undergoing microdissection of the central and bilateral neck compartments were biochemically cured, with minimal perioperative morbidity.[395,396] When repeat surgery is planned for curative intent, preoperative assessment should include locoregional imaging (ie, ultrasonography of the neck and upper mediastinum) and attempts to exclude patients with distant metastases, which may include contrast-enhanced CT or MRI of the neck, chest, and abdomen.[396]

Postoperative Management and Surveillance

Calcitonin is very useful for surveillance, because this hormone is only produced in the parafollicular cells. Thus, measurements of serum calcitonin and CEA levels are the cornerstone of postoperative assessment for residual disease (see *Surveillance* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). For patients with a detectable basal calcitonin or elevated CEA level, neck imaging is recommended. Patients with undetectable calcitonin levels can subsequently be followed with annual measurements of serum markers. Additional studies or more frequent testing can be done for those with significantly rising calcitonin or CEA. Nonetheless, the likelihood of significant residual disease is very low in patients with an undetectable basal calcitonin level in a sensitive assay. If the patient has MEN 2, annual screening for pheochromocytoma (MEN 2B or 2A) and hyperparathyroidism (MEN 2A) should also be performed. For some low-risk *RET* mutations (eg, codons 768, 790, 804, or 891), less frequent screening may be appropriate.

Patients with detectable serum markers (ie, calcitonin levels ≥150 pg/mL) should have contrast-enhanced CT or MRI of the neck, chest, and abdomen with a liver protocol. Bone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.[356] The NCCN Panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but there is insufficient evidence to recommend any particular choice or combination of tests.[356]

For the asymptomatic patient with detectable markers in whom imaging fails to identify foci of disease, the NCCN Panel recommends conservative surveillance with repeat measurement of the serum markers every 6 to 12 months. For patients who are asymptomatic with abnormal markers and repeated negative imaging, continued observation or consideration of cervical reoperation is recommended if primary surgery was incomplete. For the patient with increasing serum markers, more frequent imaging may be considered. Outside of clinical trials, no therapeutic intervention is recommended on the basis of abnormal markers alone.

Recurrent or Persistent Disease

For the 2014 update, a new section on kinase inhibitors was added to the algorithm (see *Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer* in the in the NCCN Guidelines for Thyroid Carcinoma). Although kinase inhibitors may be recommended for patients with MTC, it is important to note that kinase inhibitors may not be appropriate for patients with stable or slowly progressive indolent disease.[397,398] Vandetanib and cabozantinib are oral receptor kinase inhibitors that increased PFS in patients with metastatic MTC.[301,303,399-401]

Vandetanib is a multitargeted kinase inhibitor; it inhibits RET, vascular endothelial growth factor (VEGFR), and endothelial growth factor receptor (EGFR).[301] In a phase III randomized trial in unresectable, locally advanced, or metastatic MTC (n = 331), vandetanib increased PFS when compared with placebo (hazard ratio [HR], 0.46; 95% CI, 0.31–0.69; $P < .001$); overall survival data are not yet available.[301] The FDA approved the use of vandetanib for patients with locally advanced or metastatic MTC who are not eligible for surgery and whose disease is causing symptoms or growing.[300] However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity.[402] The NCCN Panel recommends vandetanib (category 1) for patients with recurrent or persistent MTC (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[301]

Cabozantinib is a multitargeted kinase inhibitor that inhibits RET, VEGFR2, and MET. In a recent phase III randomized trial (EXAM) in patients with locally advanced or metastatic MTC (n=330), cabozantinib increased median PFS when compared with placebo (11.2 vs. 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; $P < .001$); overall survival data are not yet available.[303] The FDA recently approved the use of cabozantinib for patients with progressive, metastatic MTC.[302,303,403,404] The NCCN Panel recommends cabozantinib (category 1) based on the phase III randomized trial and FDA approval (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Rare adverse events with cabozantinib include severe bleeding and gastrointestinal perforations or fistulas; severe hemorrhage is a contraindication for cabozantinib.

When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended with (or without) postoperative EBRT. For unresectable locoregional disease that is symptomatic or structurally progressive, the following treatment can be considered: 1) EBRT; 2) vandetanib (category 1); or 3) cabozantinib

(category 1). Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include: 1) palliative resection, ablation (eg, radiofrequency, embolization), or other regional treatment; 2) vandetanib (category 1); or 3) cabozantinib (category 1) (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but observation is acceptable given the lack of data regarding alteration in outcome.

In the setting of disseminated symptomatic metastases, the NCCN Panel recommends the following: 1) vandetanib (category 1);[301,401,405] 2) cabozantinib (category 1);[303] 3) clinical trial; or 4) consider other small molecule kinase inhibitors (ie, sorafenib or sunitinib) if clinical trials, vandetanib, or cabozantinib are not available or appropriate.[287,406-410] If the patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered, using dacarbazine or combinations including dacarbazine.[411,412] EBRT can be used for focal symptoms. Bisphosphonate therapy or denosumab can be considered for bone metastases.[339-341] Best supportive care is also recommended.

In patients with metastatic MTC, sorafenib reduces symptoms due to hypercalcitonemia and metastases.[408] In addition, clinical response was seen in 6 of 8 patients with MTC who were treated with a combination of sorafenib and the farnesyltransferase inhibitor, tipifarnib.[413] Sunitinib was associated with clinical response in several case reports.[409,414,415] Clinical trials are assessing the effectiveness of novel multitargeted therapies including sunitinib,[287,409] sorafenib,[413,416] and pazopanib.[417] Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.[304,328,330] Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.

Novel therapies and the management of aggressive MTC have been reviewed.[276,418-421] Of interest, calcitonin levels decreased dramatically after vandetanib therapy, which did not directly correlate with changes in tumor volume; thus, calcitonin may not be a reliable marker of tumor response in patients receiving RET inhibitor therapy.[405] A recent phase II trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with 131I.[422] Overall survival was improved in the subset of patients with increased calcitonin doubling times.[423]

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[424] Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[425] Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[111,425] The incidence of anaplastic thyroid carcinoma is decreasing.[424] As previously mentioned, anaplastic carcinoma is the least common type of thyroid carcinoma. Of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, only 2% had anaplastic thyroid carcinoma.[15]

Approximately 50% of patients with anaplastic thyroid carcinoma have either a prior or coexistent differentiated carcinoma. Anaplastic carcinoma develops from more differentiated tumors as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor protein.[426] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not.

Therefore, 131I imaging cannot be used and RAI treatment is not effective in these patients with anaplastic thyroid carcinoma.

Patients with anaplastic thyroid carcinoma present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[352,427] The lungs and pleura are the most common site of distant metastases (≤90% of patients with distant disease). About 5% to 15% of patients have bone metastases; 5% have brain metastases; and a few have metastases to the skin, liver, kidneys, pancreas, heart, and adrenal glands. All anaplastic thyroid carcinomas are considered stage IV (A, B, or C) (see Table 1). The T4 category includes: 1) T4a tumors that are intrathyroidal and surgically resectable; and 2) T4b tumors that are extrathyroidal and not surgically resectable. However, clinically apparent anaplastic tumors are usually unresectable.

The diagnosis of anaplastic thyroid carcinoma is usually established by core or surgical biopsy. Sometimes it is difficult to discriminate between anaplastic thyroid carcinoma and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[99,428] Diagnostic procedures include a CBC, serum calcium, TSH level, and imaging studies. CT scans of the neck can accurately determine the extent of the thyroid tumor and identify tumor invasion of the great vessels and upper aerodigestive tract structures.[429] FDG-PET scans with (or without) CT scans can be considered. Bone metastases are usually lytic.

Prognosis

No effective therapy exists for anaplastic thyroid carcinoma; it is almost uniformly fatal.[430,431] The median survival from diagnosis is about 5 months.[428,432] The 1-year survival rate is about 20%.[427,432] Death is attributable to upper airway obstruction and suffocation (often despite tracheostomy) in 50% of these patients; in the remaining patients, death is attributable to complications of local and distant disease and/or therapy.[433] Patients with disease confined to the neck at diagnosis have a mean survival of 8 months compared with 3 months if the disease extends beyond the neck.[434] Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, WBC ≥10,000 mm^3, and dyspnea as a presenting symptom.[435,436]

Treatment

Once the diagnosis of anaplastic thyroid carcinoma is confirmed, it is essential to rapidly determine whether local resection is an option.[424] However, most patients with anaplastic thyroid carcinoma have unresectable or metastatic disease. The patency of the airway should be considered throughout the patient's course.[433] If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with selective resection of all involved local or regional structures and nodes. Total thyroidectomy with attempted complete tumor resection has not been shown to prolong survival except for the few patients whose tumors are small and confined entirely to the thyroid or readily excised structures.[432,434,437,438]

EBRT can increase short-term survival in some patients; EBRT can also improve local control and can also be used for palliation (eg, to prevent asphyxiation).[390,424,428,436,439-441] Treatment with single-drug chemotherapy is not very effective, although some patients may respond or have stable disease.[428] Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year.[442] Distant metastases then become the leading cause of death. [443] Similar improvement in local disease control has been reported with a

combination of hyperfractionated RT and doxorubicin-based regimens, followed by debulking surgery in responsive patients or other multimodality approaches.[444-446] IMRT may be useful to reduce toxicity.[390,428,447-451] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival.

Systemic therapy recommendations are described in the algorithm (see *Systemic Therapy for Anaplastic Thyroid Carcinoma* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[428,452] Either concurrent chemoradiation or chemotherapy alone regimens may be used depending on the clinical setting; however, chemoradiation is generally more toxic. If using chemoradiation, the ATA Guidelines recommend using weekly chemotherapy regimens.[428] Chemotherapy alone can be considered for patients with unresectable or metastatic disease. Single-agent doxorubicin is the only agent that is approved by the FDA for anaplastic thyroid carcinoma.[428] Paclitaxel (single agent) may benefit some newly diagnosed patients; increased survival has been reported in patients with stage IVB disease.[453-455] If weekly paclitaxel is used, the ATA Guidelines recommend using paclitaxel at 60 to 90 mg/m^2 IV weekly and not the dose previously reported in the study by Ain et al.[428,455]

Given the poor outcome with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials. Clinical trials include fosbretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin (EPC2407), which are vascular disrupting agents), CS-7107 (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.[282,344,452,456-463] A patient with anaplastic thyroid carcinoma had a durable complete response in a phase I trial with CA4P, and was disease free for several years.[464,465] A study in 26 patients with advanced anaplastic thyroid carcinoma showed that 33% of patients survived more than 6 months after receiving fosbretabulin.[462] A larger trial in 80 patients (FACT) reported that the addition of fosbretabulin—to a carboplatin/paclitaxel regimen—resulted in a nonsignificant increase in median survival (5.2 vs. 4.0 months).[452,466] The trial was stopped early and did not complete the initial accrual because of the rarity of the disease and the low accrual rate. Multimodality therapy is recommended in patients with locally resectable disease (see *Primary Treatment* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[428,447,452,467-471] Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN Panel acknowledged that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported.[472] Preliminary data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in a subset of patients with anaplastic thyroid cancer who have ALK gene fusions.[473]

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