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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thyroid Carcinoma

Version 1.2021 — April 9, 2021

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 1.2021 of the NCCN Guidelines for Thyroid Carcinoma from Version 2.2020 include:

Thyroid Carcinoma

General

- Algorithms describing workup for thyroid nodule known or suspected, Bethesda I, and Bethesda II were removed from the guidelines. This information was previously noted on pages THYR-1 and THYR-2.

THYR-1

- Changed: Carcinoma or suspicious for carcinoma (Bethesda V ~~and~~ *or* VI)
- Bottom branch, added: *Consider* to Repeat FNA.

THYR-2

- Combined branches for AUS/FLUS (Bethesda III) *or* Follicular neoplasm (Bethesda IV).
- Added a middle branch for *Molecular diagnostics, not informative.* Under treatment, added options: *Nodule surveillance or Consider lobectomy or total thyroidectomy in select situations for definitive diagnosis/treatment.*
- Footnote b, added: *If molecular diagnostics are technically inadequate or not done, then repeat FNA.*
- Footnote i, changed: "lobectomy" to "*surgery*."

Papillary Carcinoma

(Note: Changes listed below have been made throughout the guideline subtypes [Follicular and Hürthle Cell Carcinoma] where appropriate for consistency)

PAP-1

- Removed footnote: ~~There is a potential role for lobectomy with or without frozen section if FNA is suspicious but not diagnostic for papillary carcinoma.~~
- Diagnostic procedures, changed:
  - Consider *assessment* ~~evaluation~~ of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy) (also applies to FOLL-1)
  - ~~Strongly consider~~ FNA for suspicious lateral neck nodes
- Footnote b, modified: Vocal cord mobility *should* ~~may~~ be examined in patients *if clinical concern for involvement, including those* with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. *Evaluation is imperative in those with voice changes.* (This change was made consistently throughout where appropriate.)
- Changed "cervical lymph node metastases" to "*lateral* cervical lymph node metastases."

PAP-2

- Combined previous pages PAP-2 and PAP-3.
- Top pathway: Macroscopic multifocal disease (>1cm) moved to middle pathway
- Middle pathway, deleted: Tumor 1-4 cm in diameter deleted
- Footnote f, changed: (<5 involved nodes with no metastasis ~~>5~~ *>2 mm* in largest dimension).
- Footnote h, modified: Measurement of thyroglobulin and antithyroglobulin antibodies may be useful for obtaining a postoperative baseline; *however, data to interpret Tg and TgAb in the setting of an intact thyroid lobe are lacking.*
- Footnote u: removed (category 2B)
- Removed footnote: May be useful for obtaining a postoperative baseline. There are not enough data to provide further recommendations.

PAP-3

- Changed: ~~Suspected or proven inadequate~~ RAI uptake *absent.*
- Changed: ~~Adequate~~ RAI uptake *present* or No RAI imaging performed.
- Footnote l, added: For contraindications to withdrawal, thyrotropin alfa may be used *as an alternative.*

PAP-4

- RAI selectively recommended (if any present), added: *Detectable anti-Tg antibodies.*
- Changed: Postoperative unstimulated Tg <~~5–~~ <10 ng/mL
- Changed: RAI ablation is not required in patients with classic PTC who have T1b/T2 (1–4 cm) N0 *or NX* ~~a and/or N0b~~ disease.
- Footnote r, added: ie, poorly differentiated, tall cell, columnar cell, hobnail variants, *diffuse sclerosing, and insular.*

Continued
UPDATES

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Updates in Version 1.2021 of the NCCN Guidelines for Thyroid Carcinoma from Version 2.2020 include:

PAP-5
- Modified: Consider pretreatment *neck imaging* ~~iodine-123 whole body diagnostic imaging with TSH stimulation(category 2B)\~~
- Removed footnote v: Alternatively, low-dose iodine-131 (1–3 mCi) may be used.

PAP-6
- Modified: *Consider* pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with TSH stimulation.

PAP-7
- Footnote x, modified: *Long-term ultrasound follow-up is not required.* A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

PAP-9
- Modified: For advanced, progressive, or threatening disease, genomic testing to identify actionable mutations (including *ALK*, NTRK, and RET gene fusions), *DNA mismatch repair (dMMR), microsatellite instability (MSI),* and tumor mutational burden (TMB).

PAP-10
- Modified: For multiple CNS lesions, consider radiotherapy, including *whole brain radiotherapy or stereotactic radiosurgery* ~~image-guided radiotherapy,~~ and/or resection in select cases.
- Footnote jj, added: Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. *Discontinuing denosumab can cause rebound atypical vertebral fractures*.

Follicular Carcinoma

FOLL-1
- Added a new footnote: *Disease monitoring is preferred in most circumstances. However, there are certain clinical scenarios in which completion of thyroidectomy may be appropriate.* (Also for HURT-1)

Medullary Carcinoma

MEDU-1
- Diagnostic Procedures:
  - Removed: Consider genetic counseling
  - Modified: Screen for germline RET proto-oncogene mutations (exons 10, 11, 13–16); *genetic counseling may be indicated.*
  - Added a new footnote: *Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.*

MEDU-2
- Modified: Screen for germline RET proto-oncogene mutations (exons 10, 11, 13–16); *genetic counseling may be indicated.*

MEDU-3
- Modified: *Consider* neck CT with contrast *if indicated.*

Anaplastic Carcinoma

ANAP-2
- *Treatment for resectable disease, added:*
  - *EBRT/IMRT with chemotherapy when clinically appropriate*
  - Footnote added: *See Principles of Radiation and RAI Therapy (THYR-C).*
- Treatment for unresectable, added:
  - *Consider molecularly targeted neoadjuvant therapy for borderline resectable disease when safe to do so.*
  - New footnote: *Regimens that may be used for neoadjuvant therapy include dabrafenib/trametinib for BRAF V600E mutations; selpercatinib or pralsetinib for RET-fusion positive tumors; and larotrectinib or entrectinib for patients with NTRK gene fusion-positive tumors.*

ANAP-3
- Treatment, added: *Consider tracheostomy*.

ANAP-A (2 of 3)
- Lenvatinib and corresponding reference were removed from the guideline.

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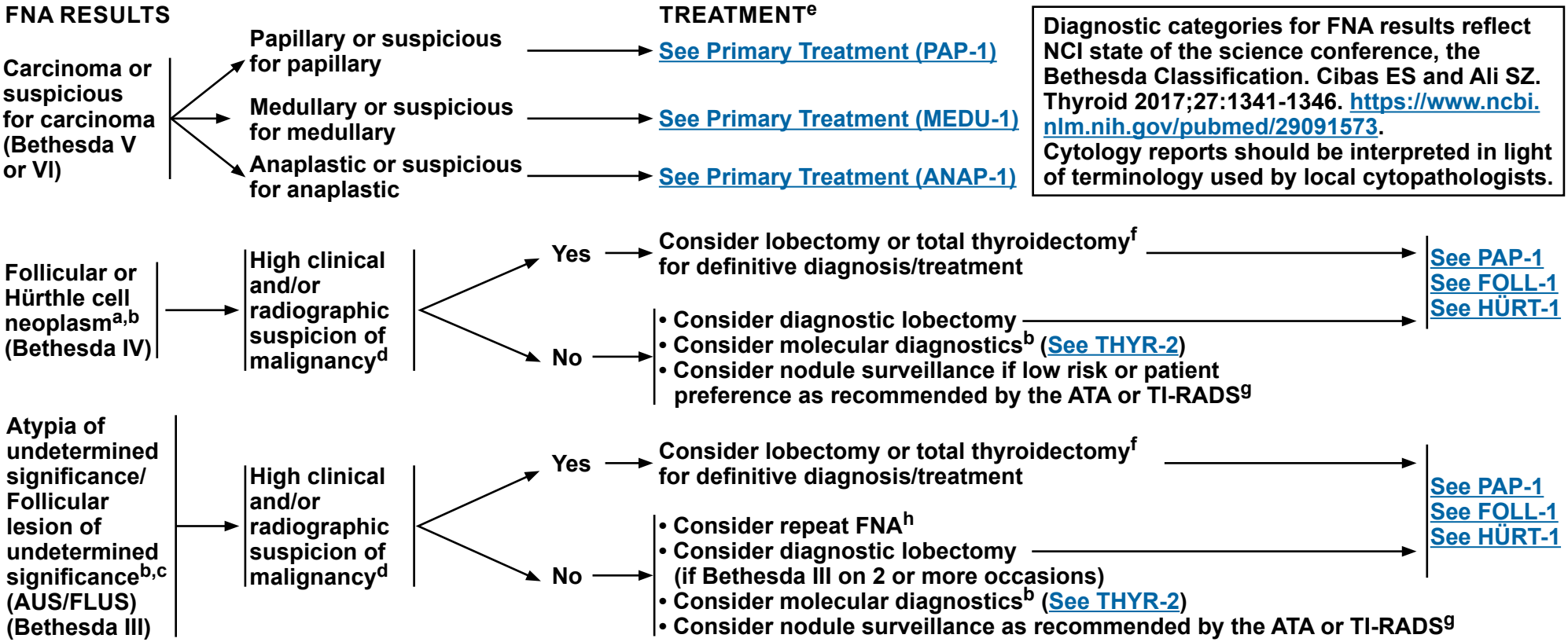

[a] Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 15%–40%. Numbers may vary by institution or cytopathologist.
[b] The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, AUS, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1. If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient. If molecular diagnostics are technically inadequate or not done, then repeat FNA.
[c] Estimated risk of malignancy is 6%–18% without NIFTP and 10%–30% with noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).
[d] Based on rapid growth of nodule, imaging, physical exam, age, clinical history of radiation, and family history.
[e] The order of the treatment options does not indicate preference.
[f] Total thyroidectomy may be considered for Hürthle cell neoplasm (Bethesda IV), history of radiation exposure, or contralateral lobe lesions.
[g] TI-RADS (https://www.jacr.org/article/S1546-1440(17)30186-2/pdf) or ATA (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4739132/pdf/thy.2015.0020.pdf).
[h] Consider second opinion pathology.

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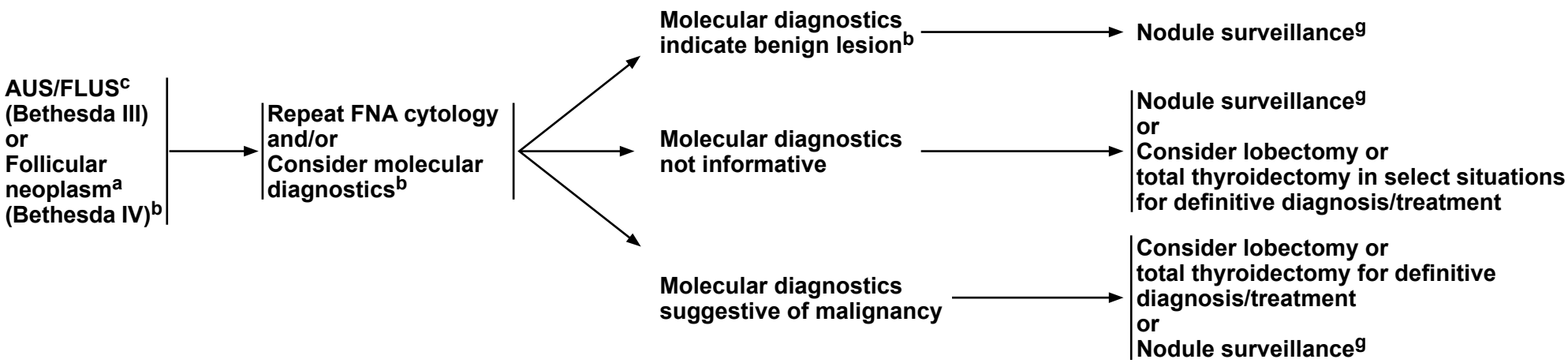

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Cibas ES and Ali SZ. Thyroid 2017;27:1341-1346. https://www.ncbi.nlm.nih.gov/pubmed/29091573. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

[a] Alternative term: Suspicious for follicular neoplasm. Estimated risk of malignancy is 15%–40%. Numbers may vary by institution or cytopathologist.

[b] The diagnosis of follicular carcinoma or Hürthle 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, AUS, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1. If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient. If molecular diagnostics are technically inadequate or not done, then repeat FNA.

[c] Estimated risk of malignancy is 6%–18% without NIFTP and 10%–30% with NIFTP.

[g] TI-RADS (https://www.jacr.org/article/S1546-1440(17)30186-2/pdf) or ATA (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4739132/pdf/thy.2015.0020.pdf).

[i] Clinical risk factors, sonographic patterns, and patient preference can help determine whether nodule surveillance or surgery is appropriate.

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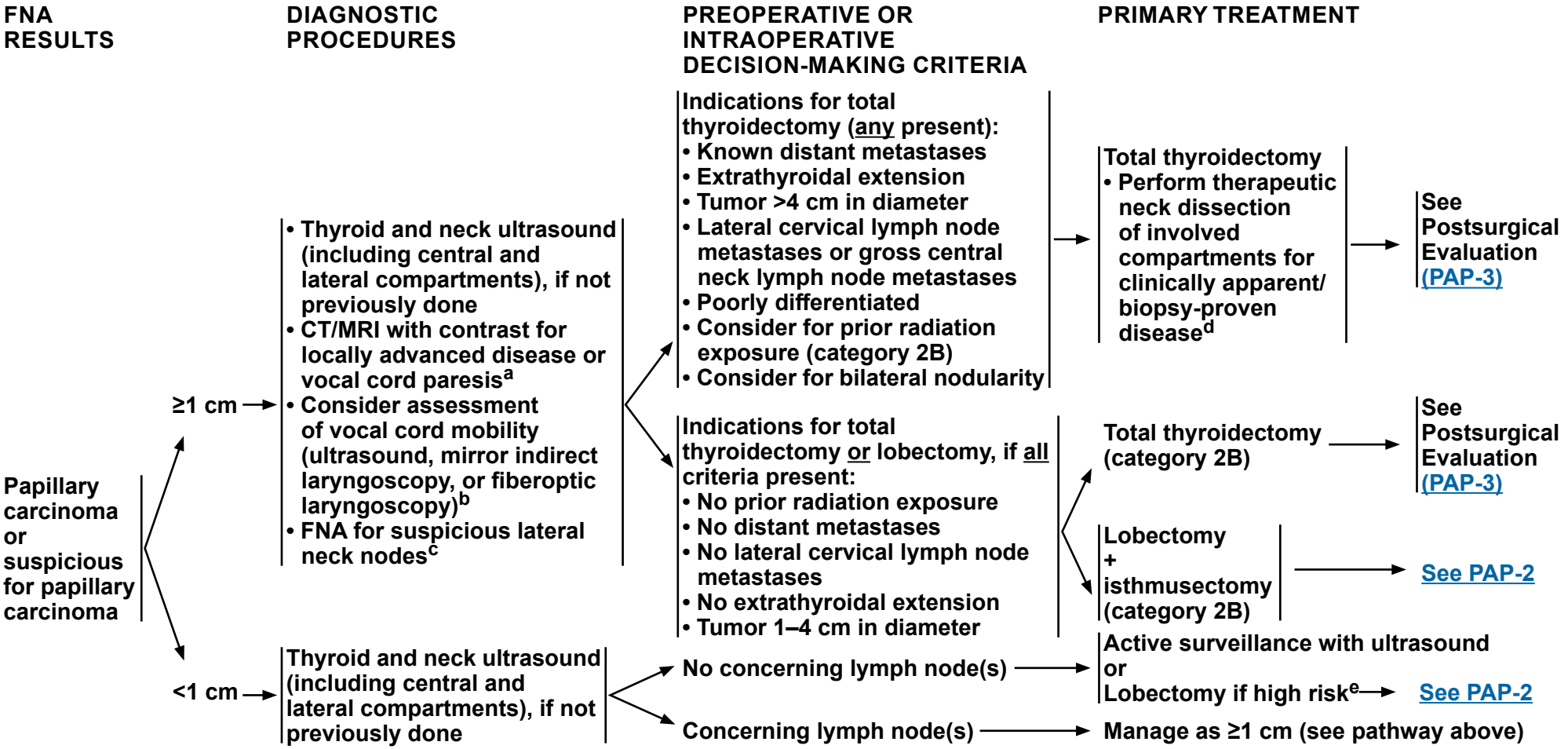

[a] Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in RAI treatment will not cause harm.
[b] Vocal cord mobility should be examined in patients if clinical concern for involvement, including those with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Evaluation is imperative in those with voice changes.
[c] Tg washout is useful in diagnosis of lymph node metastases and recommended if cytology is negative.
[d] Routine prophylactic central neck dissection is not indicated in most papillary thyroid cancers.
[e] Posterior location, abutting the trachea or apparent invasion, etc.

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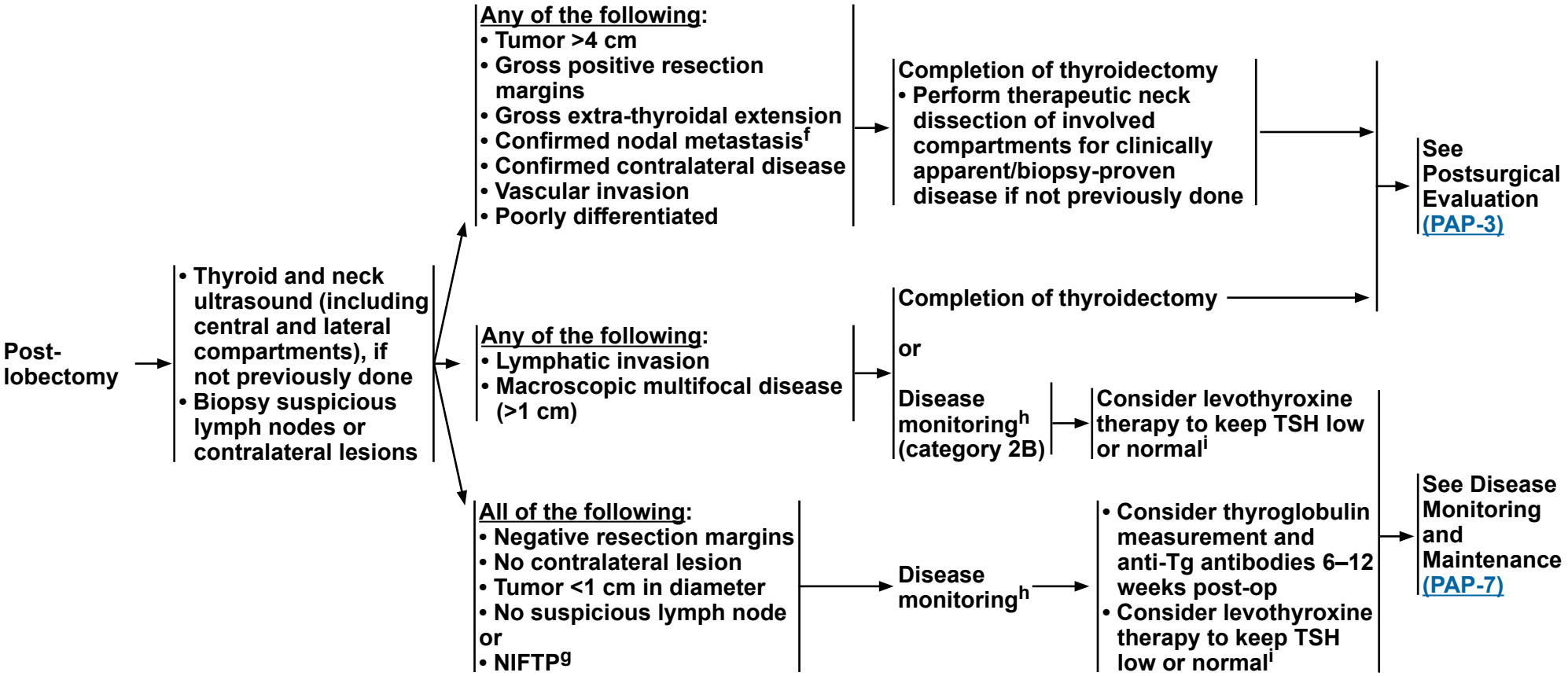

[f] Completion of thyroidectomy is not required for incidental small volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm in largest dimension). See PAP-4.
[g] Formerly called encapsulated follicular variant of PTC, NIFTP has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.
[h] Measurement of thyroglobulin and antithyroglobulin antibodies may be useful for obtaining a postoperative baseline; however, data to interpret Tg and TgAb in the setting of an intact thyroid lobe are lacking.
[i] See Principles of TSH Suppression (THYR-A).

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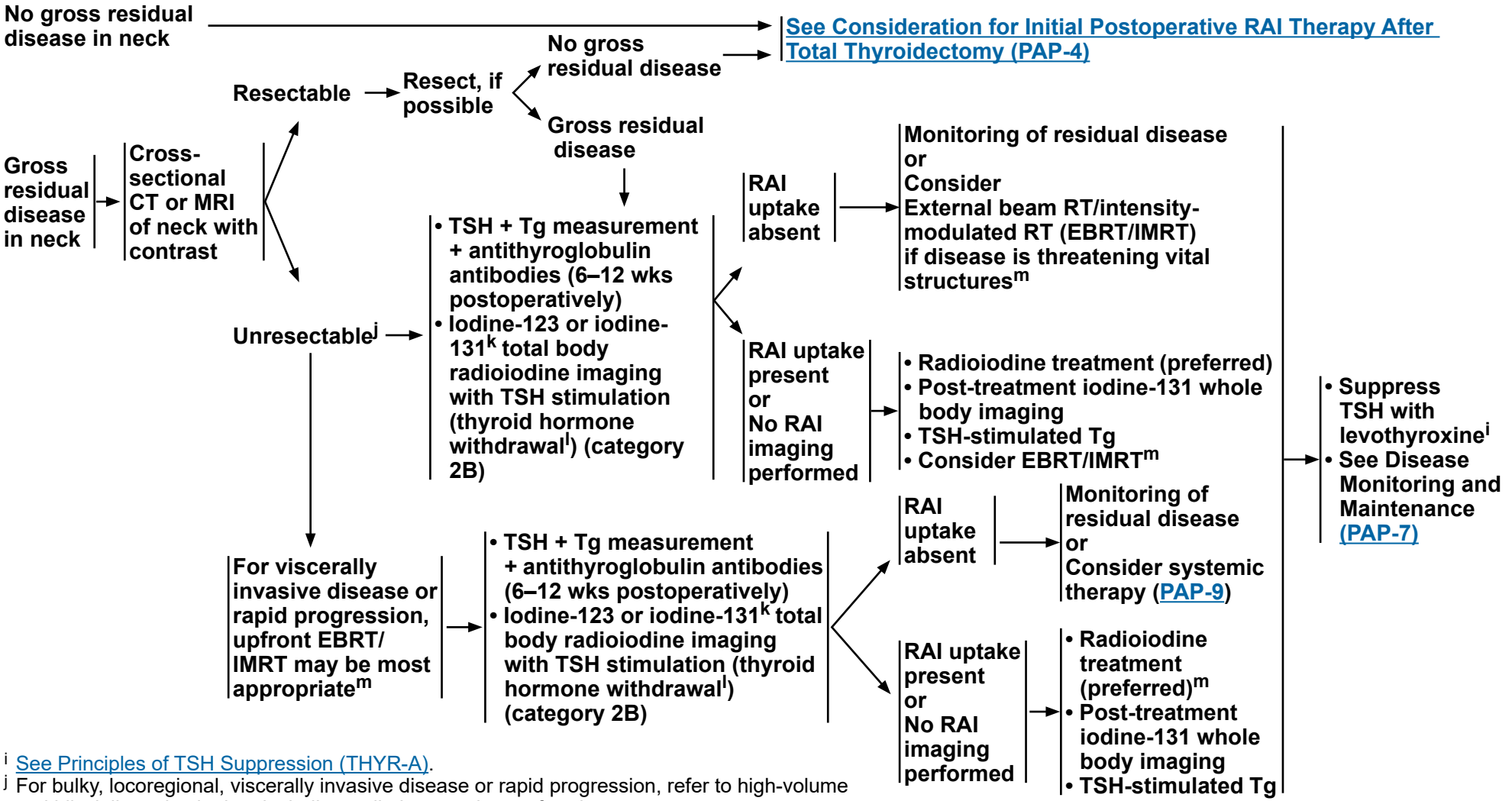
POSTSURGICAL EVALUATION



[i] See Principles of TSH Suppression (THYR-A).
[j] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.
[k] If considering dosimetry iodine-131 is the preferred agent.
[l] For contraindications to withdrawal, thyrotropin alfa may be used as an alternative.
[m] See Principles of Radiation and RAI Therapy (THYR-C).

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CLINICOPATHOLOGIC FACTORS

RAI not typically recommended (if all present):
- Classic papillary thyroid carcinoma (PTC)
- Largest primary tumor <2 cm
- Intrathyroidal
- Unifocal or multifocal (all foci ≤1 cm)
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL[n]
- Negative postoperative ultrasound, if done[o]

RAI selectively recommended (if any present):
- Detectable anti-Tg antibodies
- Largest primary tumor 2–4 cm
- High-risk histology[r]
- Lymphatic invasion
- Cervical lymph node metastases
- Macroscopic multifocality (one focus >1 cm)
- Postoperative unstimulated Tg <10 ng/mL[n]
- Microscopic positive margins

RAI typically recommended (if any present):
- Gross extrathyroidal extension
- Primary tumor >4 cm
- Postoperative unstimulated Tg >10 ng/mL[n,q]
- Bulky or >5 positive lymph nodes

Known or suspected distant metastases at presentation

Gross residual disease not amenable to RAI therapy

CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

RAI not typically indicated, See PAP-8

RAI ablation is not required in patients with classic PTC who have T1b/T2 (1–4 cm) N0 or NX disease or small-volume N1a disease (fewer than 5 metastatic lymph nodes with <2 mm of focus of cancer in node), particularly if the postoperative Tg is <1 ng/mL in the absence of interfering anti-Tg antibodies.

RAI ablation is recommended when the combination of individual clinical factors (such as the size of the primary tumor, histology, degree of lymphatic 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 PAP-6

Amenable to RAI See PAP-7

See PAP-10

[n] Tg values obtained 6–12 weeks after total thyroidectomy.
[o] If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.
[q] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.
[r] ie, poorly differentiated, tall cell, columnar cell, hobnail variants, diffuse sclerosing, and insular.

For general principles related to radioactive iodine (RAI) therapy, see the Principles of Radiation and Radioactive Iodine Therapy (THYR-C).

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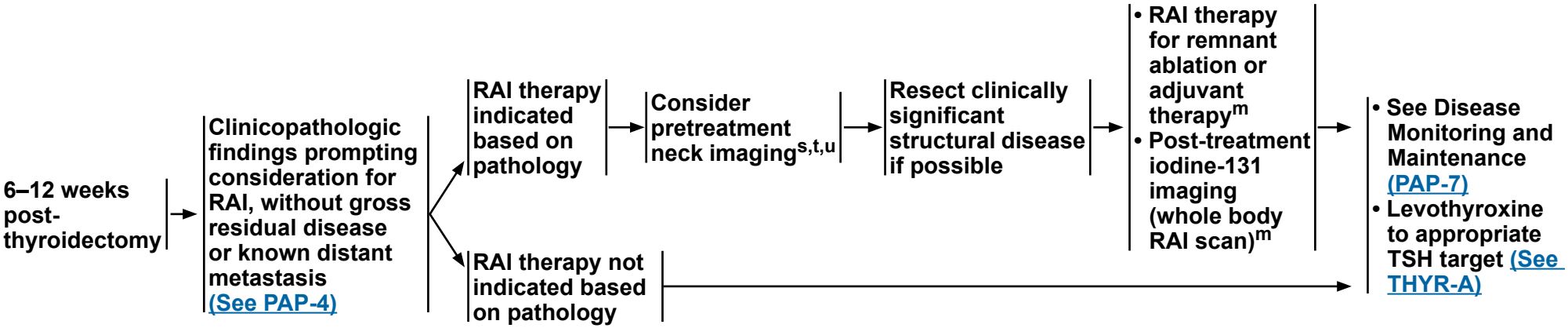
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



m See Principles of Radiation and RAI Therapy (THYR-C).
s Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.
t A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
u While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased glomerular filtration rate (GFR). Dialysis patients require special handling.

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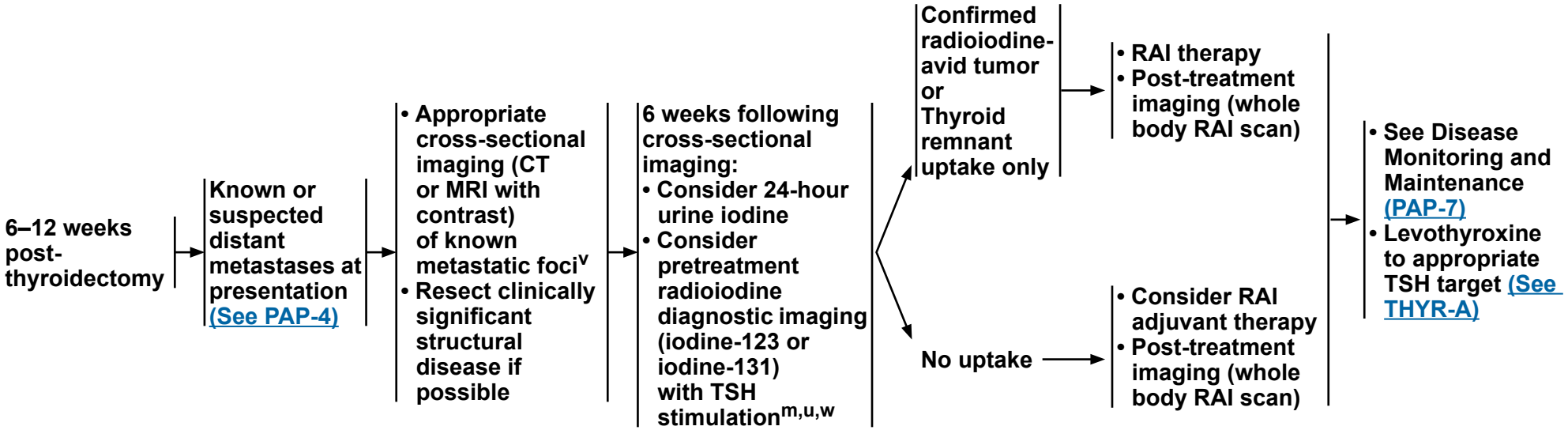
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[m] See Principles of Radiation and RAI Therapy (THYR-C).

[u] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

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

[w] Thyrotropin alfa may be used for elderly patients for when prolonged hypothyroidism may be risky.

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DISEASE MONITORING AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound[x]
- Consider TSH-stimulated or TSH-unstimulated Tg measurements using an ultrasensitive assay in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[y]
- Consider TSH-stimulated radioiodine whole body 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

FINDINGS

No evidence of disease (NED) → **Long-term disease monitoring[z]**
Patients treated with iodine-131 ablation, with a negative ultrasound, stimulated Tg <2 ng/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 (eg, CT or MRI with contrast) as clinically appropriate, may be considered if clinical suggestion of recurrent disease.
→ **Recurrent disease** (See PAP-8)

Abnormal findings → **Additional workup**
If iodine-131 imaging negative and stimulated Tg >2–5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT with contrast, chest CT with contrast, PET/CT)
→ **Recurrent disease** (See PAP-8) **or Metastatic disease** (See PAP-9)

[x] Long-term ultrasound follow-up is not required. A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[y] 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.
[z] See NCCN Guidelines for Survivorship.

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RECURRENT DISEASE

- Stimulated Tg 1–10 ng/mL and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[aa]

→ Suppress TSH with levothyroxine[i] → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (See PAP-7)

- Progressively rising Tg (basal or stimulated)
- Scans (including PET) negative

→ Consider radioiodine therapy with ≥100 mCi[bb]
and
Post-treatment iodine-131 imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy (minimum of 6–12 months between RAI treatments)

Locoregional recurrence → Consider preoperative iodine total body scan →

Surgery (preferred) if resectable[cc]
and/or
Radioiodine treatment,[bb] if radioiodine imaging positive
or
Disease monitoring for non-progressive disease that is stable and distant from critical structures
or
For select patients with unresectable, non–radioiodine-avid, and progressive disease, consider:
- EBRT (IMRT/SBRT)[m]
  and/or
- Systemic therapies (See Treatment of Metastatic Disease PAP-9)

or
For select patients with limited burden nodal disease, consider local therapies when available (ethanol ablation, radiofrequency ablation [RFA])

Metastatic disease →

RAI therapy for iodine-avid disease[m]
and/or
Local therapies when available[dd]
and/or
See PAP-9 if not amenable to RAI

[aa] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 mo after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method employed for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated thyroglobulin levels.

[bb] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).

[cc] Preoperative vocal cord assessment, if central neck recurrence.

[dd] Ethanol ablation, cryoablation, RFA, etc.

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

[m] See Principles of Radiation and RAI Therapy (THYR-C).

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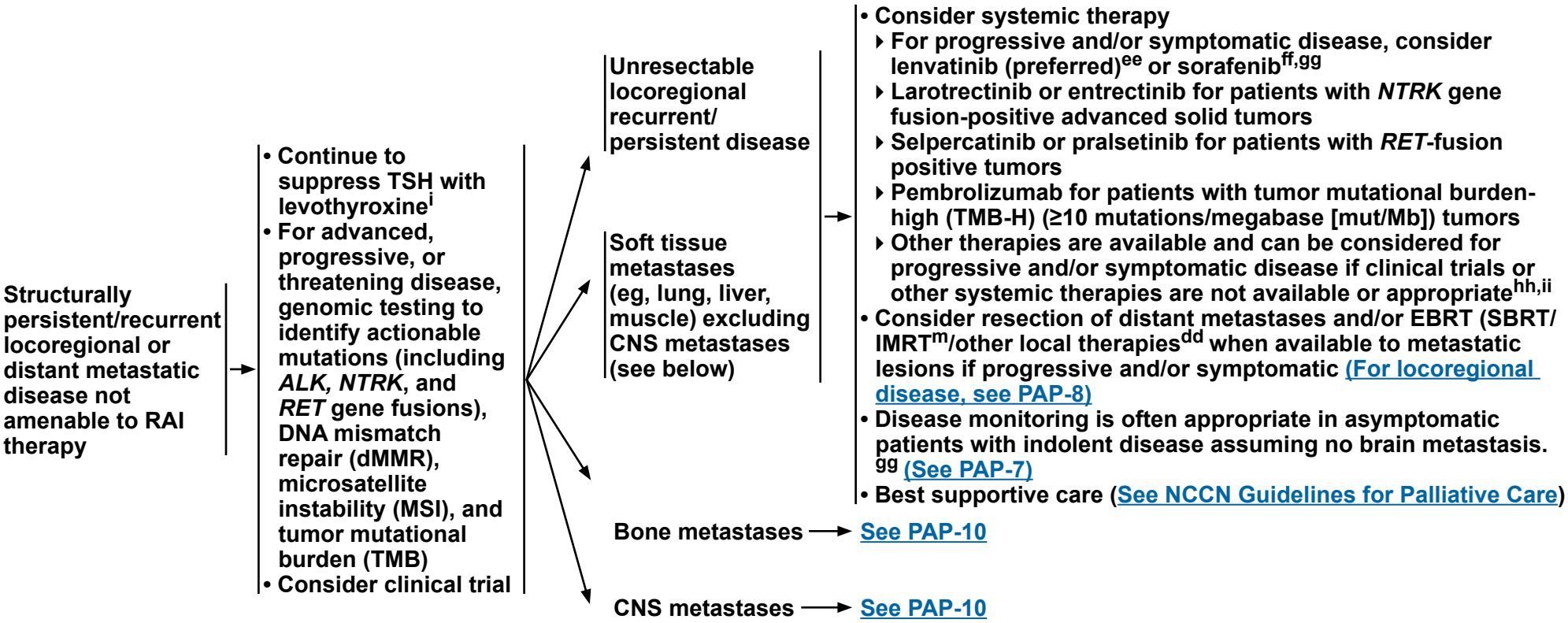
TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



[i] See Principles of TSH Suppression (THYR-A).
[m] See Principles of Radiation and RAI Therapy (THYR-C).
[dd] Ethanol ablation, cryoablation, RFA, etc.
[ee] In a subset of patients (>65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.
[ff] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[kk]

Bone metastases →

- Consider surgical palliation and/or EBRT/SBRT/other local therapies[dd] when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage.
- Consider embolization or other interventional procedures as alternatives to surgical resection/EBRT/IMRT in select cases.
- Consider intravenous bisphosphonate or denosumab.[jj]
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease.[gg] (See PAP-7)
- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.[ff]
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors.
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[gg,hh,ii]
- Best supportive care (See NCCN Guidelines for Palliative Care)

CNS metastases →

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery[m] is preferred
  or
- For multiple CNS lesions, consider radiotherapy, including whole brain radiotherapy or stereotactic radiosurgery[m], and/or resection in select cases
  and/or
- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib[ff,ll,mm]
    and/or
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
    and/or
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[gg,hh,ii,jj]
- Best supportive care (See NCCN Guidelines for Palliative Care)

[m] See Principles of Radiation and RAI Therapy (THYR-C).
[dd] Ethanol ablation, cryoablation, RFA, etc.
[ff] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[jj] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.
[kk] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[ll] After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[mm] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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NCCN Guidelines Version 1.2021
Thyroid Carcinoma – Follicular Carcinoma

NCCN Guidelines Index
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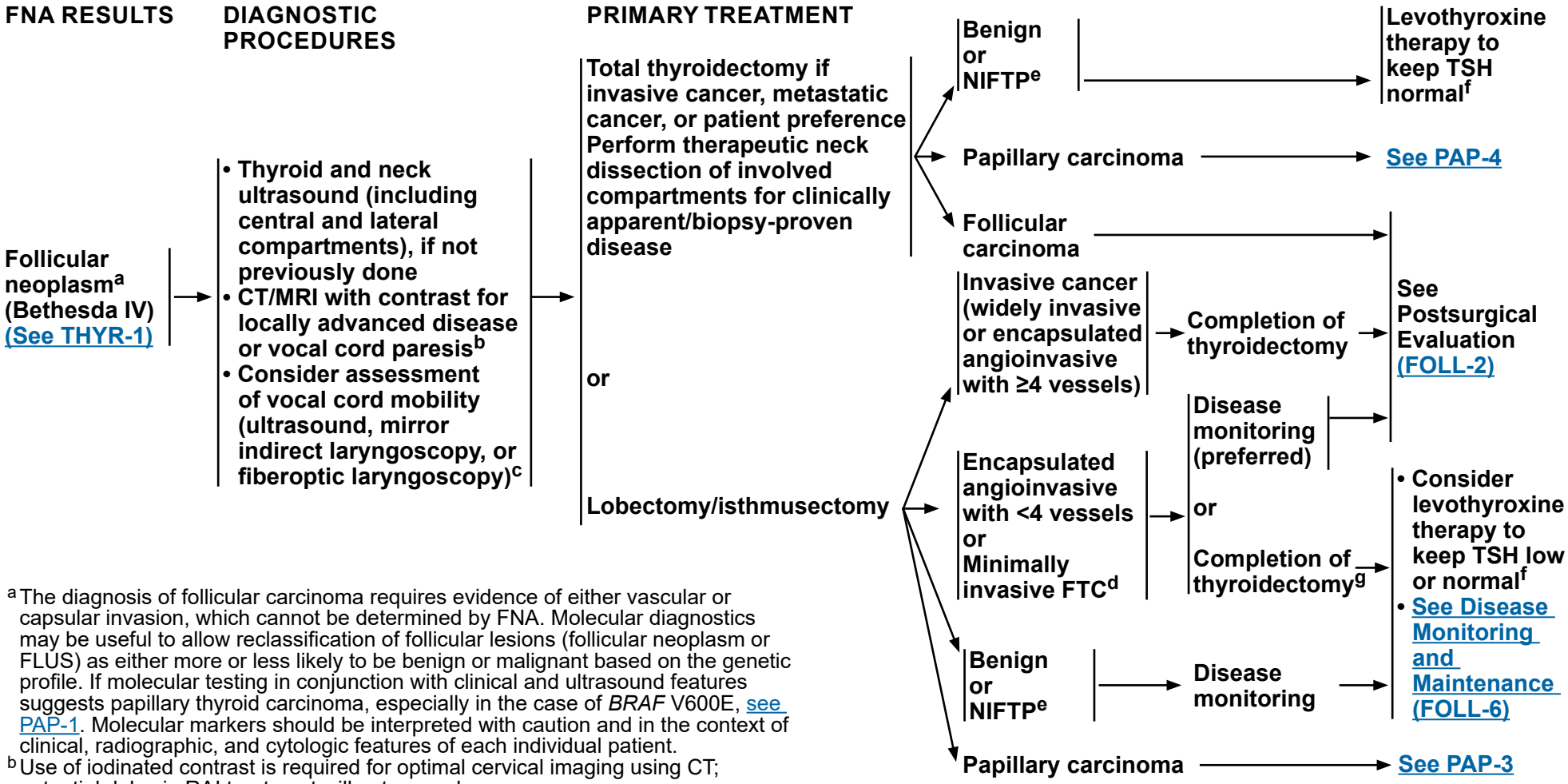
Discussion



[a] 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 FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing in conjunction with clinical and ultrasound features suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.

[b] Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in RAI treatment will not cause harm.

[c] Vocal cord mobility should be examined in patients if clinical concern for involvement, including those with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Evaluation is imperative in those with voice changes.

[d] Minimally invasive follicular thyroid carcinoma (FTC) is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

[e] Formerly called encapsulated follicular variant of PTC, NIFTP has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.

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

[g] Disease monitoring is preferred in most circumstances. However, there are certain clinical scenarios in which completion of thyroidectomy may be appropriate.

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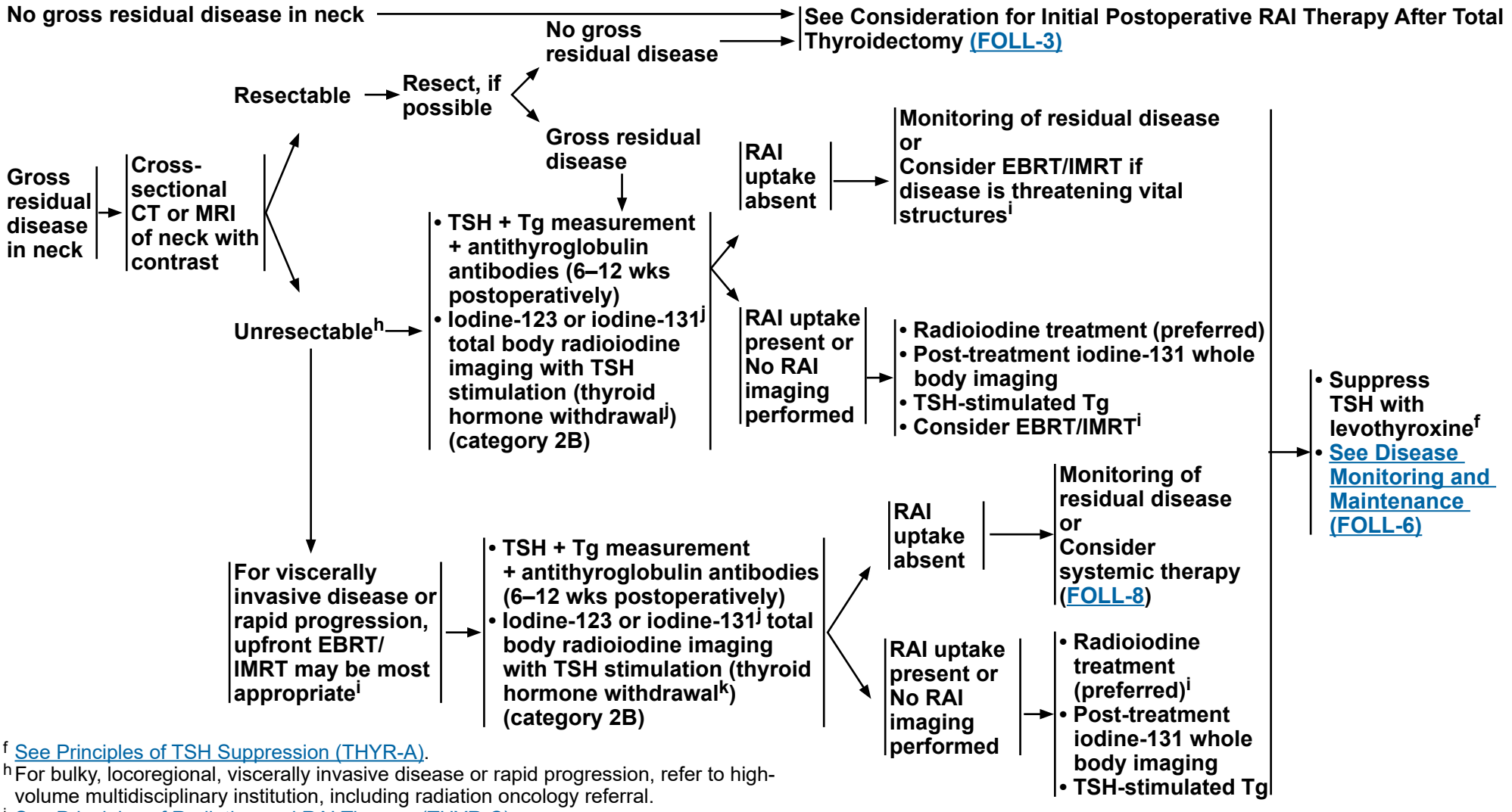
POSTSURGICAL EVALUATION



[f] See Principles of TSH Suppression (THYR-A).
[h] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.
[i] See Principles of Radiation and RAI Therapy (THYR-C).
[j] If considering dosimetry iodine-131 is the preferred agent.
[k] For contraindications to withdrawal, thyrotropin alfa may be used as an alternative.

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CLINICOPATHOLOGIC FACTORS

RAI not typically recommended (if all present):
- Largest primary tumor <2 cm
- Intrathyroidal
- No vascular invasion
- Clinical N0
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL[l]
- Negative postoperative ultrasound, if done[m]

→ **RAI not typically indicated** (See Surveillance FOLL-6)

RAI selectively recommended (if any present):
- Largest primary tumor 2–4 cm
- Minor vascular invasion[d]
- Cervical lymph node metastases
- Detectable anti-Tg antibodies
- Postoperative unstimulated Tg <10 ng/mL[l]
- Microscopic positive margins

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

RAI recommended (if any present):
- Gross extrathyroidal extension
- Primary tumor >4 cm
- Extensive vascular invasion[d]
- Postoperative unstimulated Tg >10 ng/L[l,n]
- Bulky or >5 positive lymph nodes

→ **RAI being considered, see FOLL-4**

Known or suspected distant metastases at presentation → **Amenable to RAI (See FOLL-5)**

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

CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

[d] Minimally invasive FTC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.
[l] Tg values obtained 6–12 weeks after total thyroidectomy.
[m] If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.
[n] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) 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 the Principles of Radiation and Radioactive Iodine Therapy (THYR-C)

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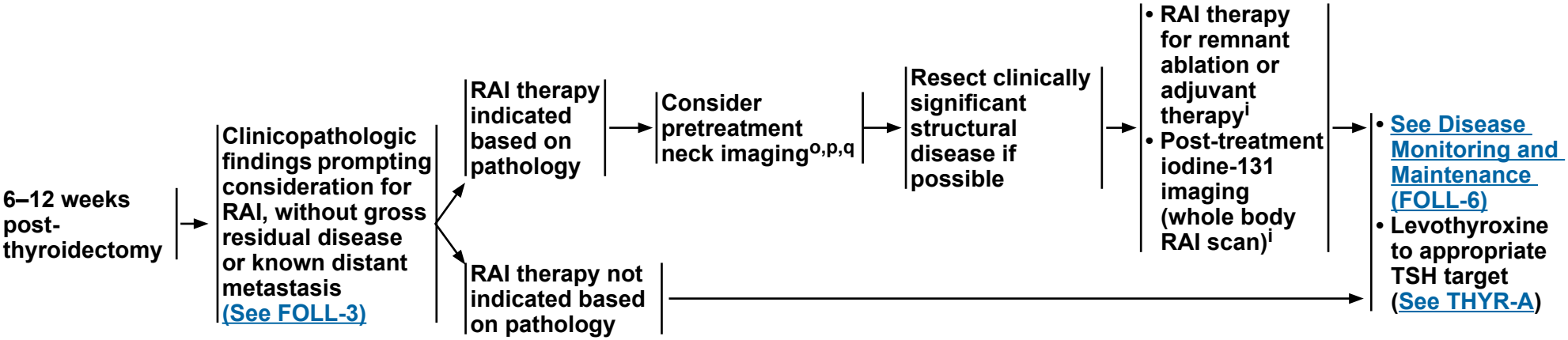
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



[i] See Principles of Radiation and RAI Therapy (THYR-C).

[o] Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

[p] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.

[q] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

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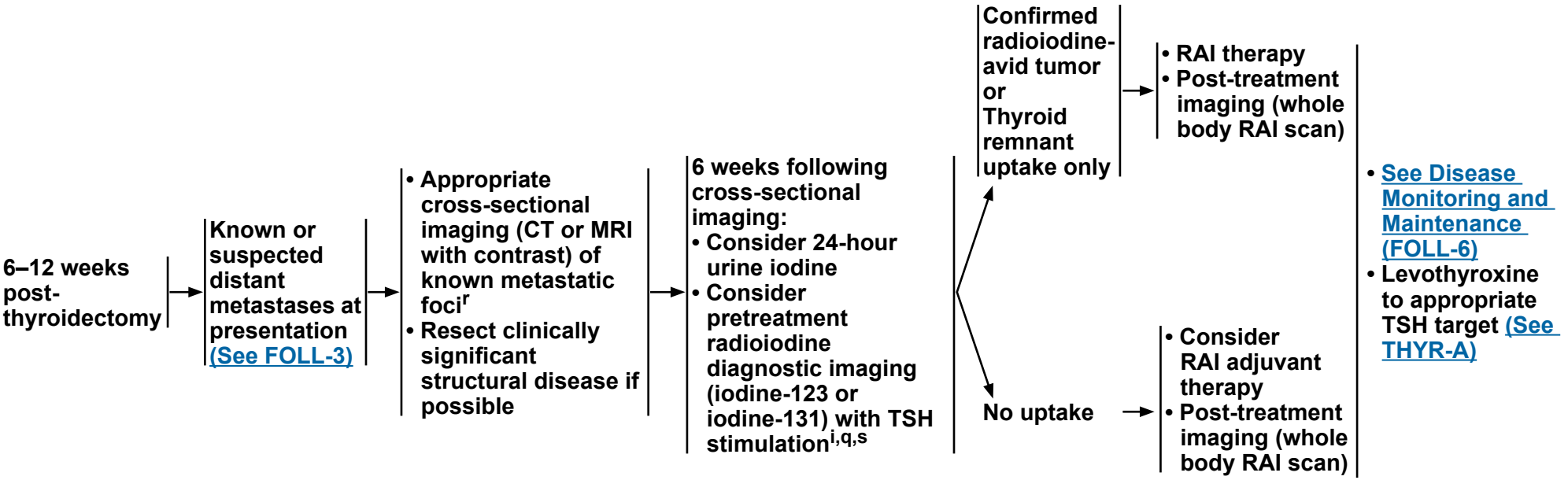
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[i] See Principles of Radiation and RAI Therapy (THYR-C).

[q] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

[r] 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 pathologic fracture either as a result of disease progression or TSH stimulation.

[s] Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

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DISEASE MONITORING AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound[t]
- Consider TSH-stimulated or TSH-unstimulated Tg measurements using an ultrasensitive assay in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[u]
- Consider TSH-stimulated radioiodine whole body 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

FINDINGS

NED →

MANAGEMENT

Long-term disease monitoring[v]
- Patients treated with iodine-131 ablation, with a negative ultrasound, stimulated Tg <2 ng/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 (eg, CT or MRI with contrast) as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

→ Recurrent disease (See FOLL-7)

Abnormal findings →

Additional workup
If iodine-131 imaging negative and stimulated Tg >2–5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT with contrast, chest CT with contrast, PET/CT)

→ Recurrent disease (See FOLL-7) or Metastatic disease (See FOLL-8)

[t] Long-term ultrasound follow-up is not required. A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[u] 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.
[v] See NCCN Guidelines for Survivorship.

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RECURRENT DISEASE

- Stimulated Tg 1–10 ng/mL and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[w]

→ Suppress TSH with levothyroxine[f] → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (See FOLL-6)

- Progressively rising Tg (basal or stimulated)
- Scans (including PET) negative

→ Consider radioiodine therapy with ≥100 mCi
and
Post-treatment iodine-131 imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy (minimum of 6–12 months between RAI treatments)

Locoregional recurrence → Consider preoperative iodine total body scan →

Surgery (preferred) if resectable[y]
and/or
Radioiodine treatment,[z] if radioiodine imaging positive
or
Disease monitoring for non-progressive disease that is stable and distant from critical structures
or
For select patients with unresectable, non–radioiodine-avid, and progressive disease, consider:
- EBRT (IMRT/SBRT)[h]
  and/or
- Systemic therapies (See Treatment of Metastatic Disease FOLL-8)

or
For select patients with limited burden nodal disease, consider local therapies when available (eg, ethanol ablation, RFA)

Metastatic disease →

RAI therapy for iodine-avid disease[i]
and/or
Local therapies when available[aa]
and/or
See FOLL-8 if not amenable to RAI

[w] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 mo after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method employed for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated thyroglobulin levels.

[y] Preoperative vocal cord assessment, if central neck recurrence.

[z] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).

[aa] Ethanol ablation, cryoablation, RFA, etc.

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

[i] See Principles of Radiation and RAI Therapy (THYR-C).

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TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy

- Continue to suppress TSH with levothyroxine[f]
- For advanced, progressive, or threatening disease, genomic testing to identify actionable mutations (including *ALK*, *NTRK*, and *RET* gene fusions), dMMR, MSI, and TMB
- Consider clinical trial

Unresectable locoregional recurrent/ persistent disease

or

Soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)

- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred)[bb] or sorafenib.[cc,dd]
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[ee,ff]
- Consider resection of distant metastases and/or EBRT (SBRT/IMRT)[i]/other local therapies[aa] when available to metastatic lesions if progressive and/or symptomatic. (For locoregional disease, see FOLL-7)
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[dd] (See FOLL-6)
- Best supportive care (See NCCN Guidelines for Palliative Care)

Bone metastases → See FOLL-9

CNS metastases → See FOLL-9

[f] See Principles of TSH Suppression (THYR-A).
[i] See Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[bb] In a subset of patients (>65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.
[cc] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[dd] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[ee] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ff] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[gg]

Bone metastases →

- Consider surgical palliation and/or EBRT/SBRT/other local therapies[aa] when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage.
- Consider embolization or other interventional procedures as alternatives to surgical resection/EBRT/IMRT in select cases.
- Consider intravenous bisphosphonate or denosumab.[hh]
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease.[dd] (See FOLL-6)
- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.[cc]
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumorss
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[dd,ee,ff]
- Best supportive care (See NCCN Guidelines for Palliative Care)

CNS metastases →

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred
  or
- For multiple CNS lesions, consider radiotherapy,[i] including whole brain radiotherapy or stereotactic radiosurgery[h], and/or resection in select cases
  and/or
- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib[cc,ii,jj]
    and/or
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
    and/or
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[dd,ee,ff,ii]
- Best supportive care (See NCCN Guidelines for Palliative Care)

[i] See Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[cc] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[dd] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
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[ff] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[gg] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[hh] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.
[ii] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[jj] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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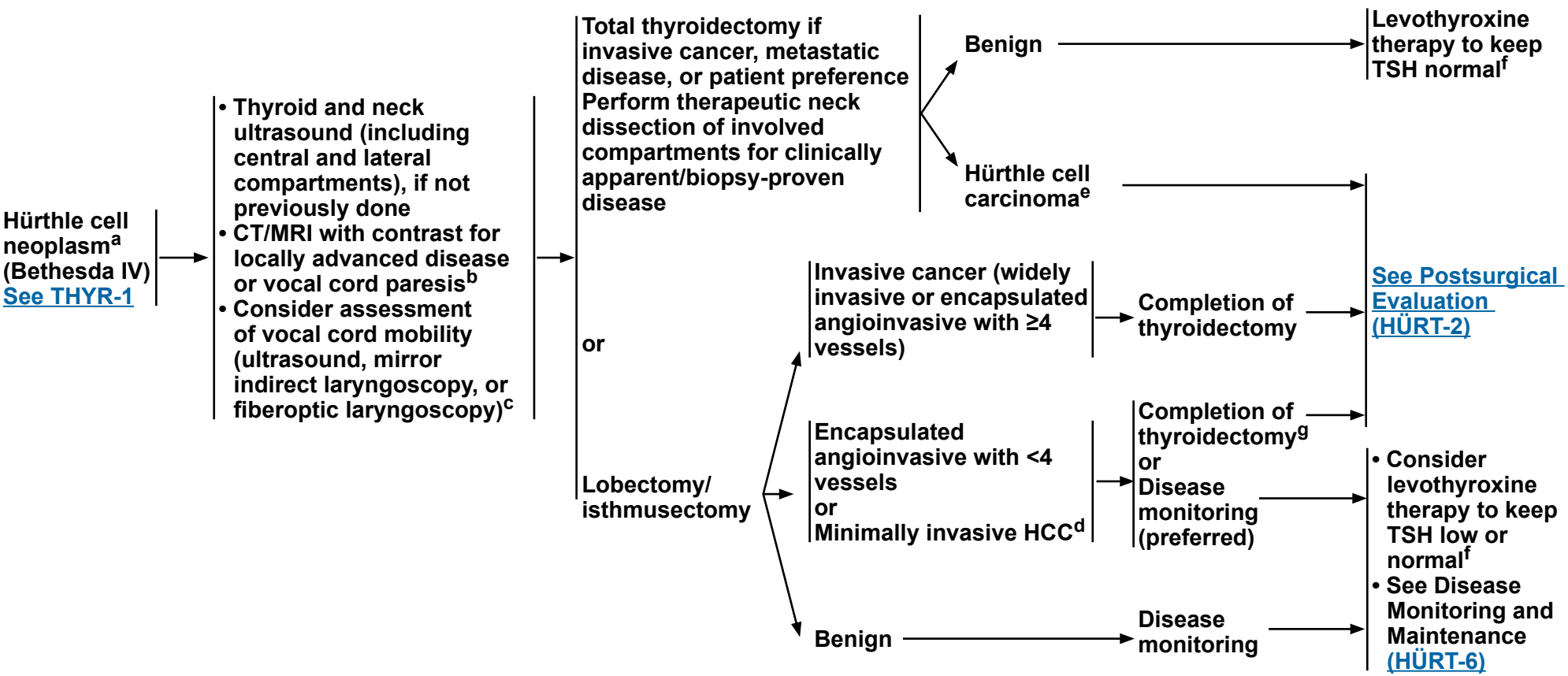

[a] The diagnosis of Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA.
[b] Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in RAI treatment will not cause harm.
[c] Vocal cord mobility should be examined in patients if clinical concern for involvement, including those with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Evaluation is imperative in those with voice changes.
[d] Minimally invasive HCC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.
[e] Also known as oxyphilic, oncocytic, or follicular carcinoma, oncocytic type.
[f] See Principles of TSH Suppression (THYR-A).
[g] Disease monitoring is preferred in most circumstances. However, there are certain clinical scenarios in which completion of thyroidectomy may be appropriate.

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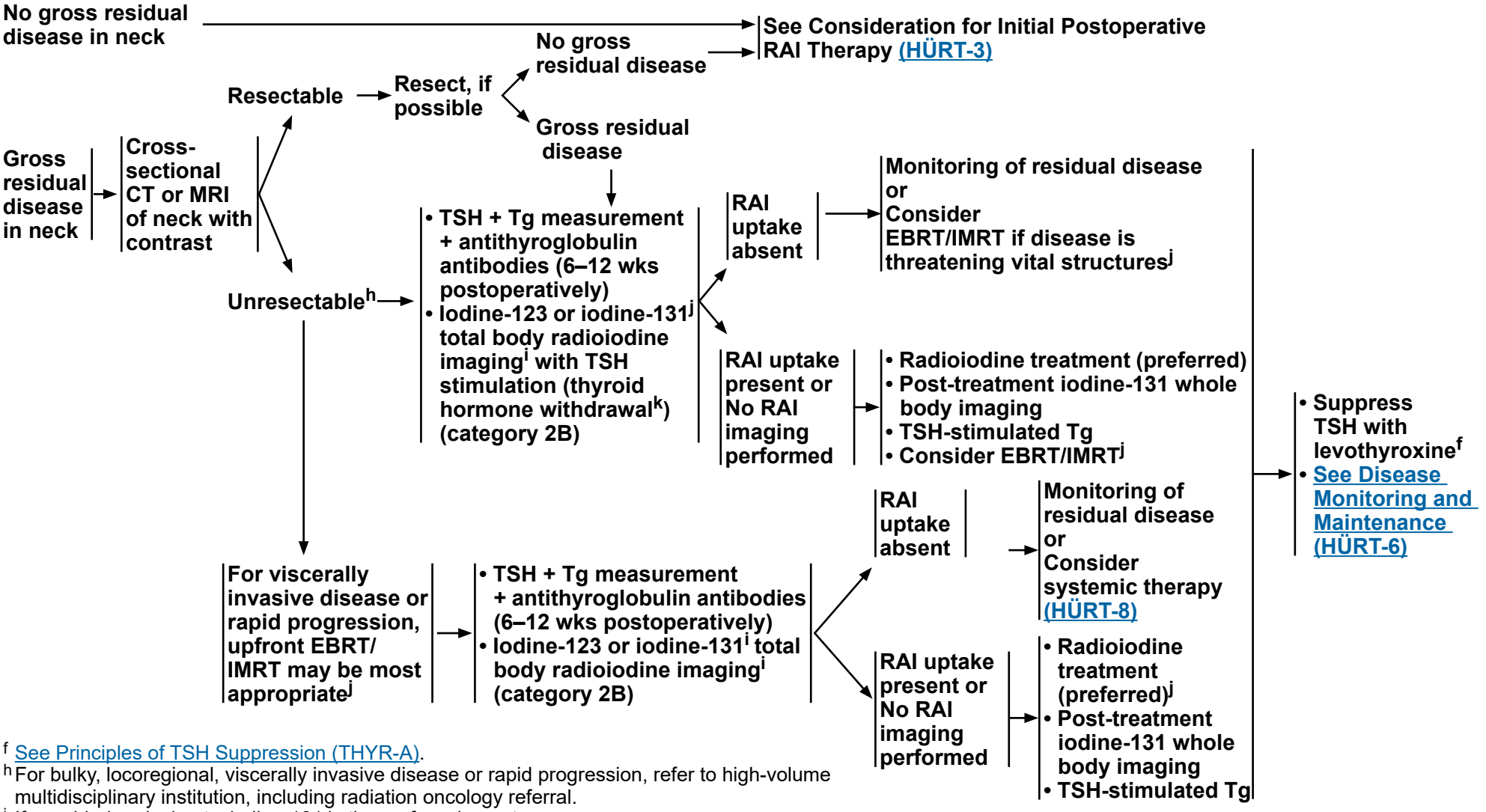
POSTSURGICAL EVALUATION



[f] See Principles of TSH Suppression (THYR-A).
[h] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.
[i] If considering dosimetry iodine-131 is the preferred agent.
[j] See Principles of Radiation and RAI Therapy (THYR-C).
[k] For contraindications to withdrawal, thyrotropin alfa may be used as an alternative.

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CLINICOPATHOLOGIC FACTORS[l]

RAI not typically recommended (if all present):
- Largest primary tumor <2 cm
- Intrathyroidal
- No vascular invasion
- Clinical N0
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL[m]
- Negative postoperative ultrasound, if done[n]

RAI selectively recommended (if any present):
- Largest primary tumor 2–4 cm
- Minor vascular invasion[d]
- Detectable anti-Tg antibodies
- Cervical lymph node metastases
- Postoperative unstimulated Tg <10 ng/mL[m]
- Microscopic positive margins

RAI recommended (if any present):
- Gross extrathyroidal extension
- Primary tumor >4 cm
- Extensive vascular invasion[d]
- Postoperative unstimulated Tg >10 ng/L[m,o]
- Bulky or >5 positive lymph nodes

CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

→ **RAI not typically indicated** (See HÜRT-6)

→ **RAI ablation is recommended when the combination of individual clinical factors (such as the size of the primary tumor, histology, degree of lymphatic 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-4)

Known or suspected distant metastases at presentation → **Amenable to RAI** (See HÜRT-5)

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

[d] Minimally invasive HCC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

[l] A majority of HCC are non–iodine-avid, particularly for high-risk disease that is negative on iodine-123/iodine-131 imaging. A negative post-therapy scan, especially done without SPECT, will likely miss distant structural disease. If Tg is high and/or pathology is high risk, FDG-PET is indicated.

[m] Tg values obtained 6–12 weeks after total thyroidectomy.

[n] If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.

[o] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) 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 the Principles of Radiation and Radioactive Iodine Therapy (THYR-C)

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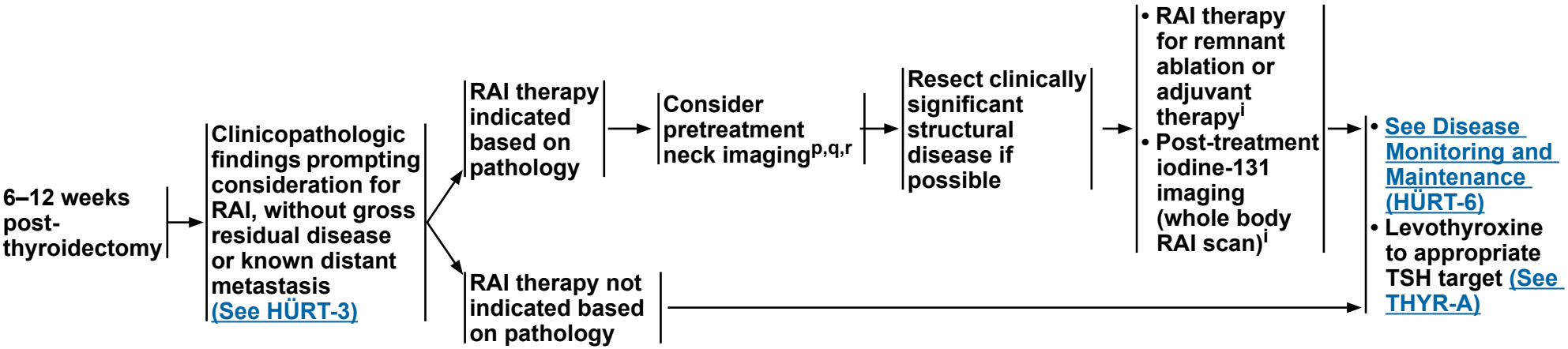
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



[i] See Principles of Radiation and RAI Therapy (THYR-C).
[p] Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.
[q] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
[r] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

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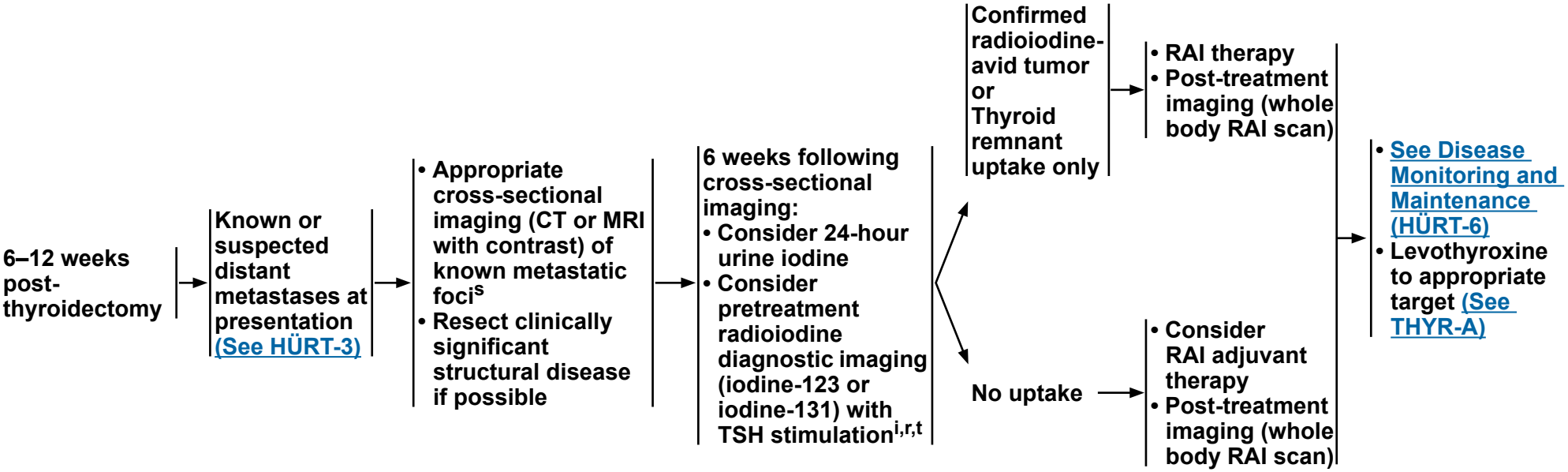
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



[i] See Principles of Radiation and RAI Therapy (THYR-C).
[r] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.
[s] To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression.
[t] Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

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DISEASE MONITORING 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 or TSH-unstimulated Tg measurements using an ultrasensitive assay in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[v]
- Consider TSH-stimulated radioiodine whole body 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

FINDINGS

NED

MANAGEMENT

Long-term disease monitoring[w]
- Patients treated with iodine-131 ablation, with a negative ultrasound, stimulated Tg <2 ng/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 (CT or MRI with contrast) as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

→ Recurrent disease (See HÜRT-7)

Abnormal findings

Additional workup
If iodine-131 imaging negative and stimulated Tg >2–5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT with contrast, chest CT with contrast, PET/CT)

→ Recurrent disease (See HÜRT-7) or Metastatic disease (See HÜRT-8)

[u] Long-term ultrasound follow-up is not required. 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.
[w] See NCCN Guidelines for Survivorship.

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RECURRENT DISEASE

- Stimulated Tg 1–10 ng/mL and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[x]

→ Suppress TSH with levothyroxine[f] → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (See HÜRT-6)

- Progressively rising Tg (basal or stimulated)
- Scans (including PET) negative

→ Consider radioiodine therapy with ≥100 mCi[z]
and
Post-treatment iodine-131 imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy (minimum of 6–12 months between RAI treatments)

Locoregional recurrence → Consider preoperative iodine total body scan →

Surgery (preferred) if resectable[aa]
and/or
Radioiodine treatment,[i] if radioiodine imaging positive
or
Disease monitoring for non-progressive disease that is stable and distant from critical structures
or
For select patients with unresectable, non–radioiodine-avid, and progressive disease, consider:
- EBRT (IMRT/SBRT)[i]
  and/or
- Systemic therapies (See Treatment of Metastatic Disease HÜRT-8)

or
For select patients with limited burden nodal disease, consider local therapies when available (eg, ethanol ablation, RFA)

Metastatic disease →

RAI therapy for iodine-avid disease[i]
and/or
Local therapies when available[bb]
and/or
See HÜRT-8 if not amenable to RAI

[x] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 mo after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method employed for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated thyroglobulin levels.

[z] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).

[aa] Preoperative vocal cord assessment, if central neck recurrence.

[bb] Ethanol ablation, cryoablation, RFA, etc.

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

[j] See Principles of Radiation and RAI Therapy (THYR-C).

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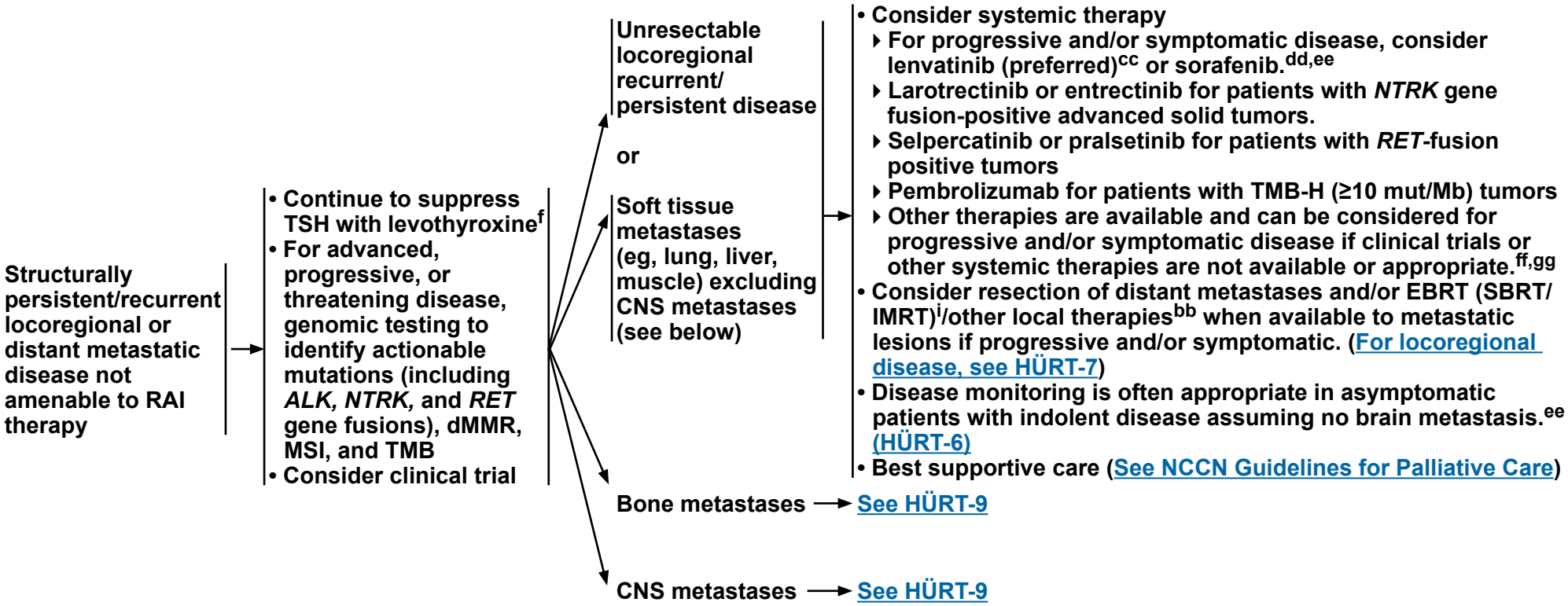
TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



[f] See Principles of TSH Suppression (THYR-A).
[i] See Principles of Radiation and RAI Therapy (THYR-C).
[bb] Ethanol ablation, cryoablation, RFA, etc.
[cc] In a subset of patients (>65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.
[dd] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[ee] Kinase inhibitor therapy may not be approriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[gg] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[hh]

Bone metastases

- Consider surgical palliation and/or EBRT/SBRT/other local therapies[bb] when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage.
- Consider embolization or other interventional procedures as alternatives to surgical resection/EBRT/IMRT in select cases.
- Consider intravenous bisphosphonate or denosumab.[ii]
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease.[ee] (HÜRT-6)
- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.[dd]
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[ee,ff,gg]
- Best supportive care (See NCCN Guidelines for Palliative Care)

CNS metastases

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery[i] is preferred
  or
- For multiple CNS lesions, consider radiotherapy,[i] including whole brain radiotherapy[i] or stereotactic radiosurgery,[i] and/or resection in select cases
  and/or
- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib[dd,jj,kk]
    and/or
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  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
    and/or
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[ee,ff,gg,jj]
- Best supportive care (See NCCN Guidelines for Palliative Care)

[i] See Principles of Radiation and RAI Therapy (THYR-C).
[bb] Ethanol ablation, cryoablation, RFA, etc.
[dd] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
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[gg] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[hh] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[ii] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.
[jj] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[kk] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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NCCN Guidelines Version 1.2021
Thyroid Carcinoma – Medullary Carcinoma

NCCN Guidelines Index
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Discussion

CLINICAL PRESENTATION

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT

Medullary thyroid carcinoma on FNA

- Basal serum calcitonin level
- CEA
- Pheochromocytoma screening[b]
- Serum calcium
- Screen for germline *RET* proto-oncogene mutations[c] (exons 10, 11, 13–16); genetic counseling may be indicated[g]
- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)[d]
- Additional cross-sectional imaging as indicated:[f]
  - Consider contrast-enhanced CT of neck/chest and liver MRI or 3-phase CT of liver[e]
  - Consider Ga-68 DOTATATE PET/CT; if not available consider bone scan and/or skeletal MRI

≥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/IMRT for grossly incomplete tumor resection when additional attempts at surgical resection have been ruled out
- Adjuvant EBRT/IMRT is rarely recommended
- 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[a,b] → **See Additional Workup and Primary Treatment (MEDU-3)**

[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[b] Evidence of pheochromocytoma should be evaluated and addressed appropriately before proceeding to the next step on the pathway.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[d] Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[e] Having distant metastases does not mean that surgery is contraindicated.
[f] Imaging may be indicated based on high burden of disease, calcitonin >400 pg/mL, or elevated CEA levels.
[g] Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.

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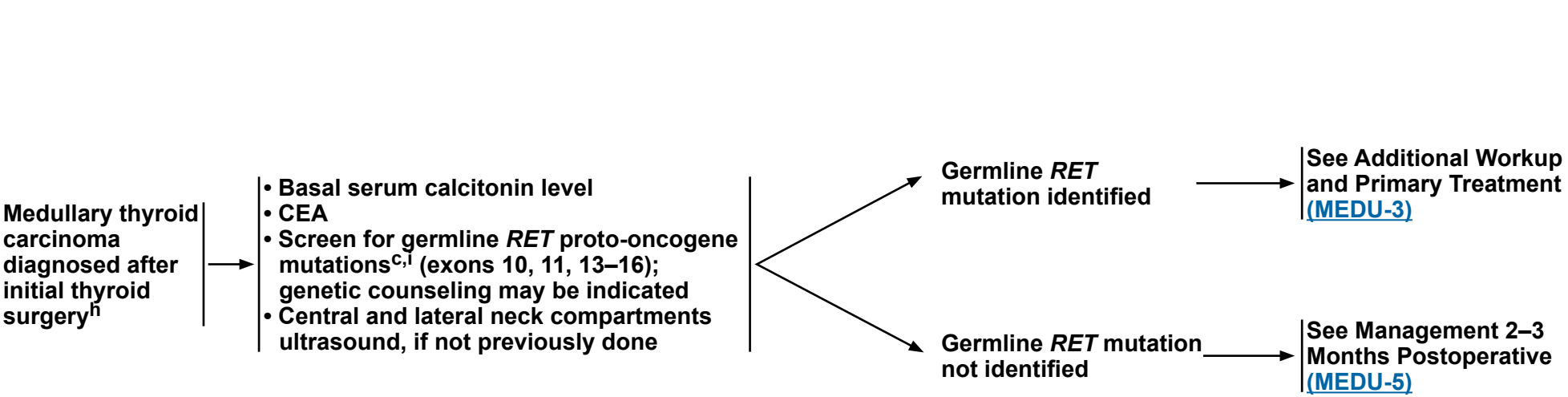

[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[h] If initial thyroid surgery was less than a total thyroidectomy, additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) may not be necessary unless there is a positive germline *RET* mutation or radiographic evidence of disease (ie, biopsy-proven residual neck disease).
[i] Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.

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NCCN Guidelines Version 1.2021
Thyroid Carcinoma – Medullary Carcinoma

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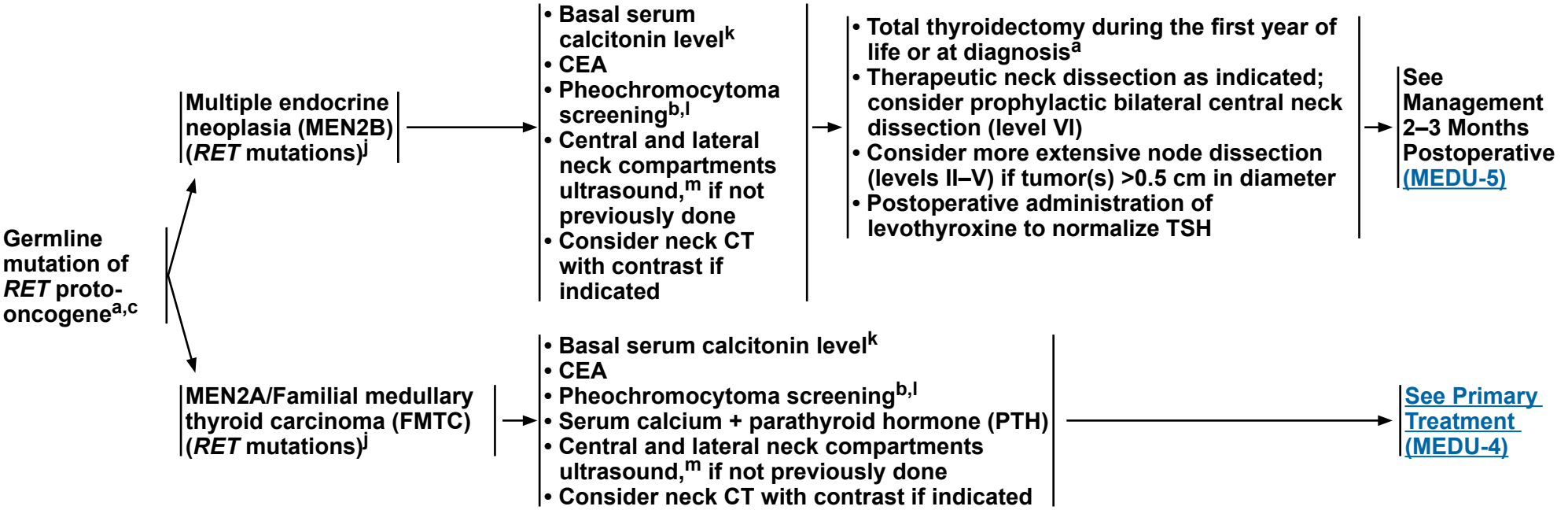

[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[b] Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[j] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other *RET* mutations associated with MEN2A or FMTC are generally moderate 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, et al. J Clin Endocrinol Metab 2001;86:5658-5671 and American Thyroid Association Guidelines Task Force. Wells SA, et al. Thyroid 2015;25:567-610.)
[k] Normal calcitonin ranges have not been established for very young children.
[l] Screening for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A) should be performed annually. For some *RET* mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.
[m] In addition to ultrasound, parathyroid imaging may include sestamibi scan with SPECT or 4D-CT depending on institutional practice/protocol.

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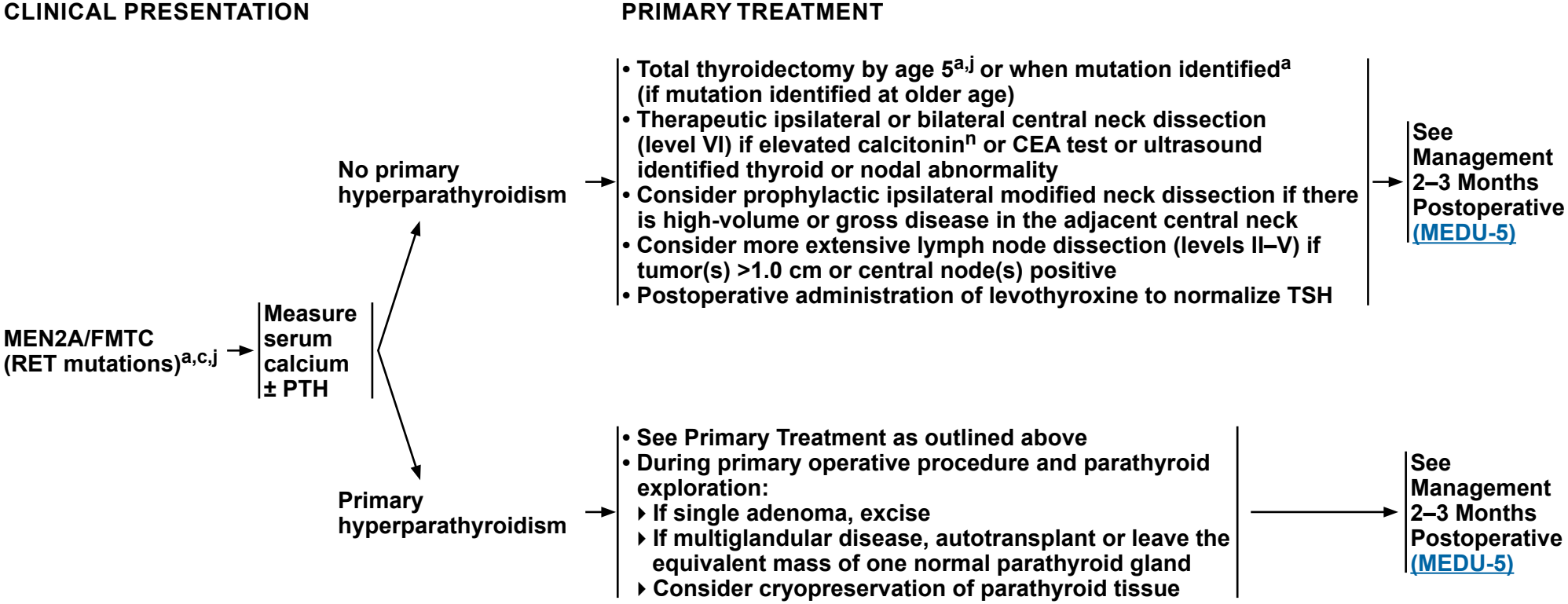

[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[j] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other *RET* mutations associated with MEN2A or FMTC are generally moderate 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, et al. J Clin Endocrinol Metab 2001;86:5658-5671 and American Thyroid Association Guidelines Task Force. Wells SA, et al. Thyroid 2015;25:567-610.)
[n] 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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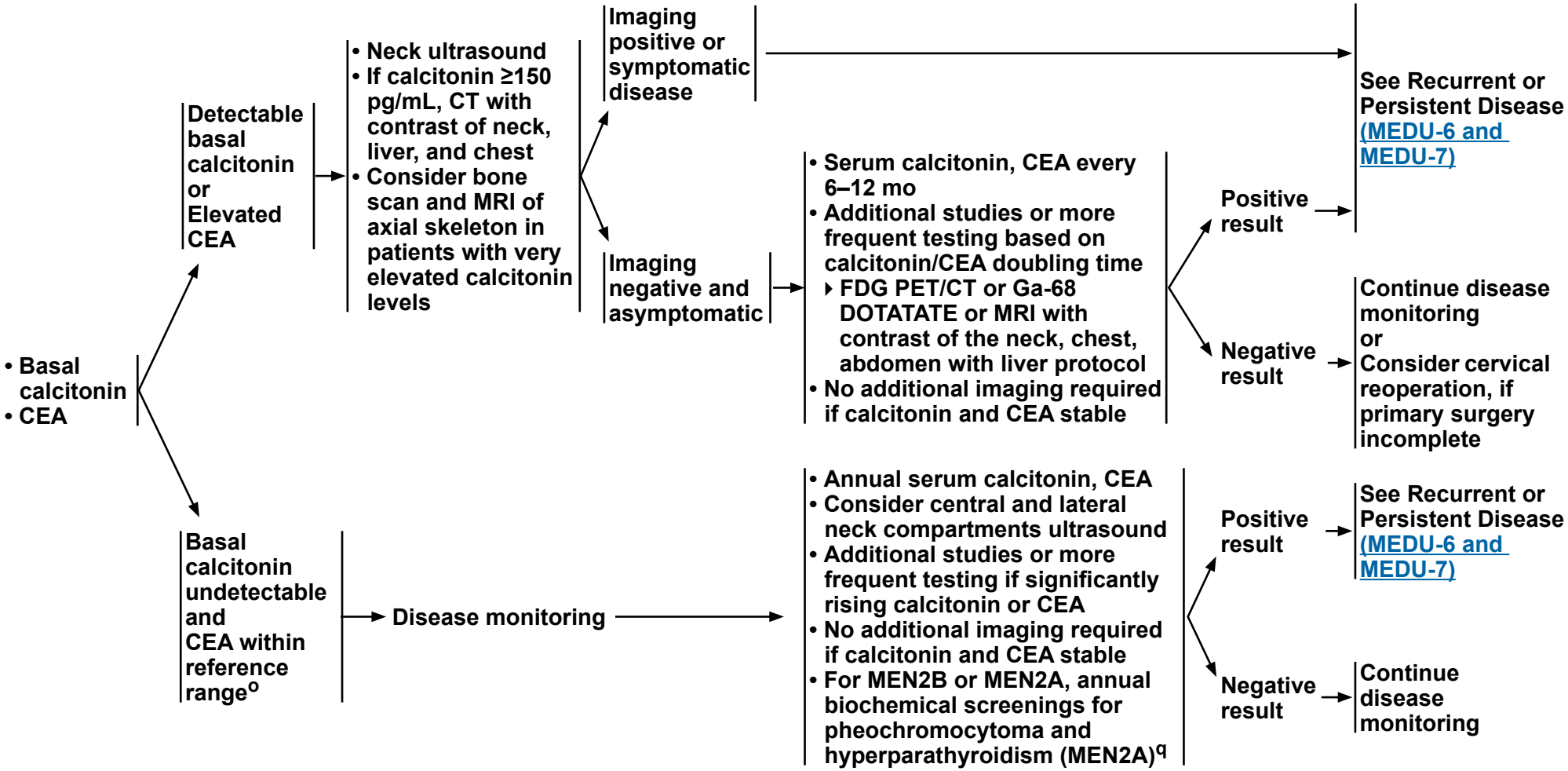
MANAGEMENT 2–3 MONTHS POSTOPERATIVE

DISEASE MONITORING[p]



[o] The likelihood of significant residual disease with an undetectable basal calcitonin is very low.
[p] See NCCN Guidelines for Survivorship.
[q] See page PHEO-1 from the NCCN Guidelines for Neuroendocrine and Adrenal Tumors.

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RECURRENT OR PERSISTENT DISEASE TREATMENT
LOCOREGIONAL DISEASE

Locoregional →

- **Surgical resection is the preferred treatment modality**
- **EBRT/IMRT can be considered for unresectable disease or, less commonly, after surgical resection**
- **Consider systemic therapy[r] for unresectable disease that is symptomatic or progressing by RECIST criteria[u,v]**
  - **Preferred Regimens**
    - ◊ **Vandetanib[s] (category 1)**
    - ◊ **Cabozantinib (category 1)**
    - ◊ **Selpercatinib (*RET* mutation-positive)[t]**
    - ◊ **Pralsetinib (*RET* mutation-positive)[t]**
  - **Useful in Certain Circumstances**
    - ◊ **Pembrolizumab (TMB-H [≥10 mut/Mb])[t]**
- **Disease monitoring**

→ **Recurrent or Persistent Disease; Distant Metastases (See MEDU-7)**

[r] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[s] 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.
[t] Genomic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.
[u] 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 Carcinoma (THYR-B).
[v] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

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RECURRENT OR PERSISTENT DISEASE
DISTANT METASTASES

Asymptomatic disease →

- **Disease monitoring**
- **Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy)**
- **Systemic therapy[r] if not resectable and progressing by RECIST criteria[u,v]**
  - **Preferred Regimens**
    - ◊ **Vandetanib[s] (category 1)**
    - ◊ **Cabozantinib (category 1)**
    - ◊ **Selpercatinib (*RET* mutation-positive)[t]**
    - ◊ **Pralsetinib (*RET* mutation-positive)[t]**
  - **Useful in Certain Circumstances**
    - ◊ **Pembrolizumab (TMB-H [≥10 mut/Mb])[t]**

→ **Progressive disease, see pathway below**

Symptomatic disease or progression[u] →

- **Systemic therapy or clinical trial**
  - **Preferred Regimens**
    - ◊ **Vandetanib (category 1)[w]**
    - ◊ **Cabozantinib (category 1)[w]**
    - ◊ **Selpercatinib (*RET* mutation-positive)[t]**
    - ◊ **Pralsetinib (*RET* mutation-positive)[t]**
  - **Other Recommended Regimens**
    - ◊ **Consider other small-molecule kinase inhibitors[x]**
    - ◊ **Dacarbazine (DTIC)-based chemotherapy[y]**
  - **Useful in Certain Circumstances**
    - ◊ **Pembrolizumab (TMB-H [≥10 mut/Mb])[t]**
- **EBRT/IMRT for local symptoms**
- **Consider intravenous bisphosphonate or denosumab[z] therapy for bone metastases**
- **Consider palliative resection, ablation (eg, RFA, embolization, other regional therapy), or other regional treatment**
- **Best supportive care**

[r] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[s] Only health care professionals and pharmacies certified through the vandetanib REMS program, a restricted distribution program, will be able to prescribe and dispense the drug.
[t] Genomic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.
[u] 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 Carcinoma (THYR-B).
[v] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.
[w] Clinical benefit can be seen in both sporadic and familial MTC.
[x] While not FDA approved for treatment of medullary thyroid cancer, other commercially available small-molecule kinase inhibitors (such as sorafenib, sunitinib, lenvatinib, or pazopanib) can be considered if clinical trials or preferred systemic therapy options are not available or appropriate, or if the patient progresses on preferred systemic therapy options.
[y] Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine or fluorouracil/dacarbazine alternating with fluorouracil/streptozocin.
[z] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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NCCN Guidelines Version 1.2021
Thyroid Carcinoma – Anaplastic Carcinoma

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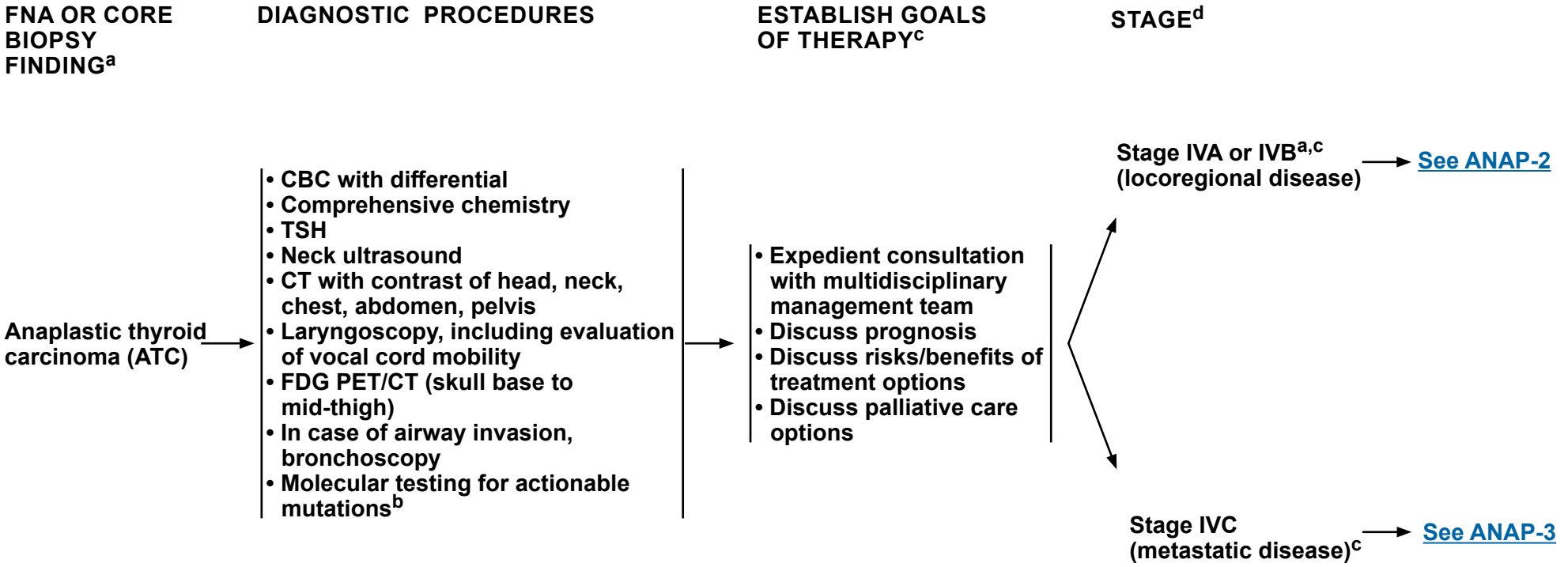

[a] Consider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary in order to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and lymphoma.
[b] Molecular testing should include *BRAF, NTRK, ALK*, *RET*, *MSI, dMMR*, and tumor mutational burden.
[c] Preoperative evaluations need to be completed as quickly as possible and involve integrated decision-making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.
[d] See Staging (ST-1).

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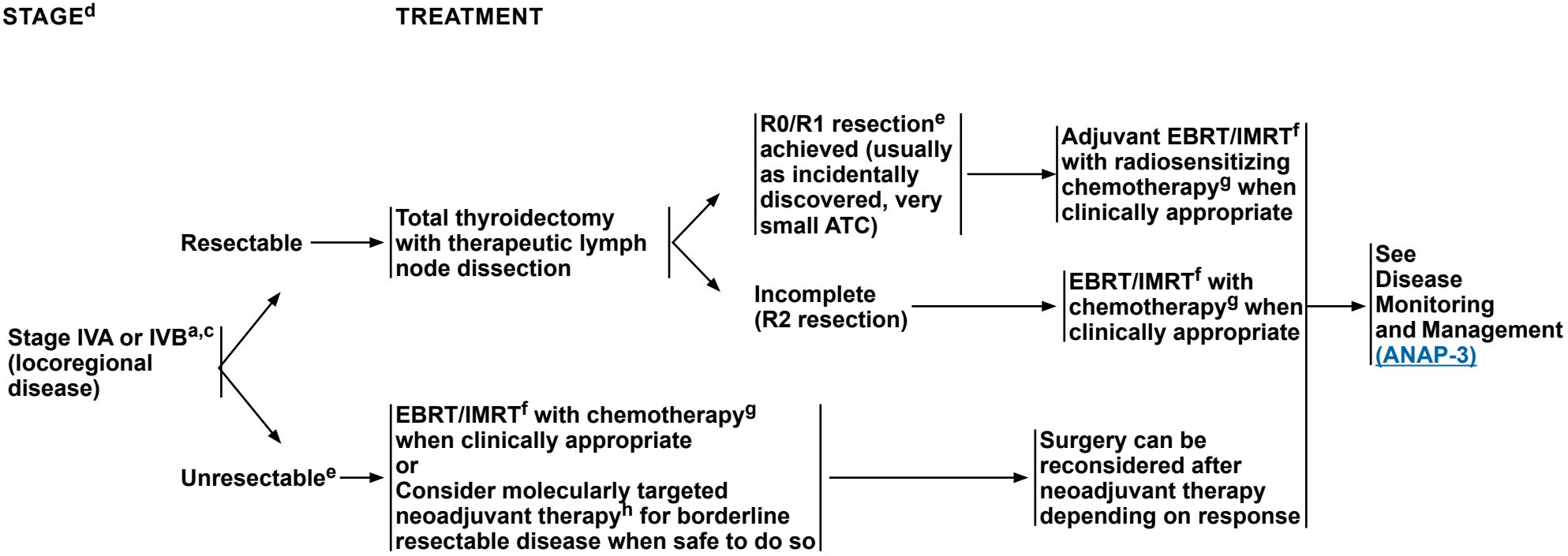

[a] Consider core or open biopsy if FNA is “suspicious” for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary in order to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and lymphoma.
[c] Preoperative evaluations need to be completed as quickly as possible and involve integrated decision-making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.
[d] See Staging (ST-1).
[e] 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.
[f] See Principles of Radiation and RAI Therapy (THYR-C).
[g] See Adjuvant/Radiosensitizing Chemotherapy Regimens for Anaplastic Thyroid Carcinoma (ANAP-A [1 of 3]).
[h] Regimens that may be used for neoadjuvant therapy include dabrafenib/trametinib for *BRAF* V600E mutations; selpercatinib or pralsetinib for RET-fusion positive tumors; and larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive tumors.

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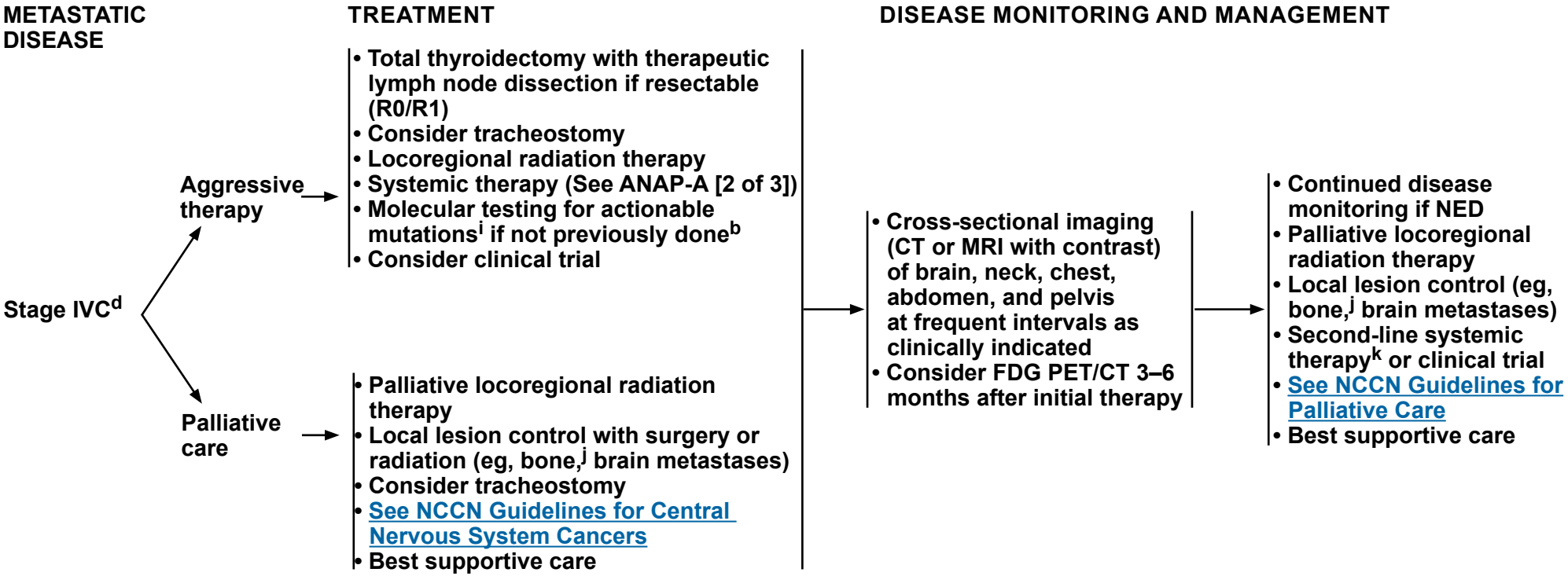

[b] Molecular testing should include *BRAF, NTRK, ALK*, *RET*, *MSI, dMMR*, and tumor mutational burden.
[d] See Staging (ST-1).
[i] Consider dabrafenib/trametinib if *BRAF* V600E mutation positive (Subbiah V, et al. J Clin Oncol 2018;36:7-13); larotrectinib or entrectinib if *NTRK* gene fusion positive (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282); selpercatinib or pralsetinib if *RET* fusion positive (Wirth L, et al. Presented at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27-October 1, 2019. Oral presentation.); or pembrolizumab for TMB-H (Marabelle A, et al. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019).
[j] Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[k] See Systemic Therapy Regimens for Metastatic Disease (ANAP-A [2 of 3]).

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SYSTEMIC THERAPY

Adjuvant/Radiosensitizing Chemotherapy Regimens[1]		
Other Recommended Regimens		
Paclitaxel/carboplatin	**Paclitaxel 50 mg/m², carboplatin AUC 2 IV**	**Weekly**
Docetaxel/doxorubicin	**Docetaxel 60 mg/m² IV, doxorubicin 60 mg/m² IV (with pegfilgrastim)** **or** **Docetaxel 20 mg/m² IV, doxorubicin 20 mg/m² IV**	**Every 3–4 weeks** **Weekly**
Paclitaxel	**30–60 mg/m² IV**	**Weekly**
Cisplatin	**30–40 mg/m² IV**	**Weekly**
Doxorubicin	**60 mg/m² IV** **or** **20 mg/m² IV**	**Every 3 weeks** **Weekly**

For Systemic Therapies for Metastatic Disease see ANAP-A (2 of 3).

[1] Adapted with permission from Mary Ann Liebert, Inc., Smallridge RC, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1124.

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SYSTEMIC THERAPY

Systemic Therapy Regimens for Metastatic Disease		
Preferred Regimens		
Dabrafenib/trametinib[2] (*BRAF* V600E mutation positive)	**Dabrafenib 150 mg PO** and **Trametinib 2 mg PO**	**Twice daily** **Once daily**
Larotrectinib[3] (*NTRK* gene fusion positive)	**100 mg PO**	**Twice daily**
Entrectinib[4] (*NTRK* gene fusion positive)	**600 mg PO**	**Once daily**
Pralsetinib[5] (*RET* fusion positive)	**400 mg PO**	**Once daily**
Selpercatinib[6] (*RET* fusion positive)	**120 mg PO (< 50 kg)** or **160 mg PO (≥50 kg)**	**Twice daily**
Other Recommended Regimens		
Paclitaxel/carboplatin[1]	**Paclitaxel 60–100 mg/m^2, carboplatin AUC 2 IV** or **Paclitaxel 135–175 mg/m^2, carboplatin AUC 5–6 IV**	**Weekly** **Every 3–4 weeks**
Docetaxel/doxorubicin[1]	**Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (with pegfilgrastim)** or **Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV**	**Every 3–4 weeks** **Weekly**
Paclitaxel[1]	**60–90 mg/m^2 IV** or **135–200 mg/m^2 IV**	**Weekly** **Every 3–4 weeks**
Doxorubicin[1]	**60–75 mg/m^2 IV** or **20 mg/m^2 IV**	**Every 3 weeks** **Weekly**
Useful in Certain Circumstances		
Pembrolizumab[7] (TMB-H [≥10 mut/Mb])	**200 mg IV** or **400 mg IV**	**Every 3 weeks** **Every 6 weeks**

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References

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SYSTEMIC THERAPY REFERENCES

[1] Adapted with permission from Mary Ann Liebert, Inc., Smallridge RC, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1121.
[2] Subbiah V, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36(1):7-13.
[3] Drilon A, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378(8):731-739.
[4] Doebele RC, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
[5] Subbiah et al. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020
[6] Wirth L, et al. Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET-altered thyroid cancers. Presented at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27-October 1, 2019. Oral presentation.
[7] Marabelle A, et al. Association of tumor mutational burden with outcomes in patients with select advanced solid tumors treated with pembrolizumab in KEYNOTE-158. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019.

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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 (0.5–2 mU/L).**
  - **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 risks and benefits 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 CARCINOMA[1-7]

- **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 radioiodine-refractory differentiated thyroid cancer (DTC).**

- **When considering kinase inhibitor therapy for individual patients, several factors should be considered.**
  - **Kinase inhibitor therapy can be associated with improved 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 drug-induced 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; side effects have been fatal. In addition, dose modification may be required, including dose holds and dose reductions.**

- **Molecular testing has been shown to be beneficial when making targeted therapy decisions, particularly related to drug therapies or clinical trial participation. In addition, the presence of some mutations may have prognostic importance.**

[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.
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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
IODINE-131 ADMINISTRATION

General Principles

Patients may be withdrawn from thyroid hormone to allow adequate elevation of TSH (>30 mU/l),[1] or prepared using 2 consecutive daily intramuscular injections of thyrotropin alfa for initial iodine-131 ablation of post-surgical gland remnant and/or treatment of locoregional residual or recurrent disease.

- **Preparation with hormone withdrawal: duration of time off thyroid hormone depends on the extent of thyroidectomy and approach to hormone replacement in the initial postoperative setting. Because of the half-life of endogenous thyroid hormone, 4–6 weeks are required for clearance following total thyroidectomy. Consequently, if no thyroid hormone is given following total thyroidectomy in an euthyroid patient, endogenous TSH levels should be sufficiently elevated (>30) in 3–6 weeks.**
- **Thyroid hormone withdrawal is preferred for most patients with distant metastatic disease based on the likelihood of augmentation of the delivered radiation dose. While thyrotropin alfa is not FDA-approved for treatment of distant metastases, it has been studied in this setting in retrospective cohorts and its use may be considered for patients unable to withdraw from thyroid hormone based on comorbidities and other clinical considerations.[2,3]**
- **Regardless of preparation method, an iodine-restricted diet is recommended for 10–14 days prior to iodine-131 therapy. A review of recent clinical history is advised to confirm the absence of recent iodinated contrast administration, amiodarone therapy over the past year, or long-acting iodine contaminants. Dietary supplements such as fish oil and daily multivitamins containing iodine should also be withheld over this period. Most common contrast media for CT require a 2-month period between contrast administration and iodine scintigraphy for adequate washout. If available, a 24-hour urine collection should be performed to confirm a normal free iodine (<100 mcg/24 h) prior to the initiation of the iodine-restricted diet. The diet involves a 10- to 14-day reduction in intake of iodized salt, seafood, and dairy products with the intention of optimizing the sensitivity of diagnostic exams and the efficacy of potential therapies that may follow. Excellent resource information can be found at ThyCa.org and LIDLifeCommunity.org.**
- **Documentation of negative pregnancy test or infertility status is required for female patients of reproductive age prior to administration of radioiodine therapy.**
- **Adherence to all local, state, and national regulatory guidelines including signed informed consent and signed written directive from an authorized user should be confirmed.**
- **Written guidelines for minimizing exposure to others should be provided for patient signature, as per national and state regulatory requirements.**
- **Pre-treatment radioiodine imaging may be considered and a post-treatment iodine-131 whole body scan should be performed in all cases.**
- **Pre-therapy whole body scans may be obtained using 2–4 mCi iodine-123 or 1–2 mCi iodine-131. Iodine-123 avoids stunning and has favorable imaging characteristics. Low activity (1–3 mCi) iodine-131 minimizes stunning and has a longer physical half-life that will permit delayed imaging to improve lesion detection while permitting dosimetry in cases where dose maximization is considered. If iodine-131 is utilized then the time between the scanning and therapy doses should ideally by <48–72 hours to avoid "stunning" from the diagnostic dose.**
- **Patients with high (>1000 mCi) cumulative lifetime administered activities should be monitored for myelosuppression and potential long-term toxicities, and although rare this should be considered in a risk-benefit analysis for use of RAI, as with any other therapy.**

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
IODINE-131 ADMINISTRATION

Administered Activity

See special circumstances below for pediatric dose adjustment.

- Remnant ablation:
  - 30–50 mCi
    - ◊ If RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, in the absence of other adverse pathologic, laboratory, or imaging features, 30 mCi of iodine-131 is recommended (category 1) following either thyrotropin alfa stimulation or thyroid hormone withdrawal. This 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 5 lymph node metastases <2 mm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.[4,5]
- Adjuvant therapy:
  - 50–100 mCi
    - ◊ For higher likelihood of residual disease based on operative pathology or pretherapy radioiodine scan
- Treatment of known disease
  - 100–200 mCi
    - ◊ For proven unresectable or metastatic disease based on pathology or pretherapy radioiodine scan
  - Dosimetry can be used to determine maximal dose at high-volume centers for documented nonresectable, large-volume, iodine-concentrating, residual, or recurrent disease. Generally, the maximum 48-hour whole-body dose should not exceed ~80 mCi to avoid pulmonary fibrosis in the case of diffuse lung metastases, and the bone marrow retention maximum should not exceed ~120 mCi at 48 hours.[1]

Special Circumstances

- Pediatric patients:
  - Chest imaging using non-contrast CT prior to treatment to assess for lung metastases
  - Weight-based dose adjustment for pediatric patients assuming routine dosing for 70 kg adult (ie, a 150 mCi dose for a 70 kg adult would translate to 2.15 mCi/kg for the pediatric patient)[6]

Special Circumstances

- RAI after imaging study or procedure using iodine contrast agent:
  - Wait 2 months to allow for free iodine levels to decrease (<100 mcg/24 hours) and allow for optimal RAI uptake[7,8]
  - Consider measurement of 24-hour urine iodine to confirm a normal free iodine prior to preparing for dosing.
- Breastfeeding patients:
  - Wait 3–6 months after cessation of lactation or with normalization of serum prolactin levels.
  - Complete cessation of breastfeeding after iodine-123 or iodine-131 administration for the current infant. There should be no increased risk to mother or infant for breastfeeding with subsequent births assuming no radioiodine is administered around the subsequent birth/breastfeeding period.[9]
- Decreased GFR/end-stage renal disease (ESRD)/hemodialysis:
  - Special consideration to administered dose, and timing with respect to dialysis to maximize therapeutic effect and minimize non-thyroid uptake/exposure[10]
  - Multidisciplinary involvement including close monitoring by radiation safety to coordinate administration, monitoring, and minimization of exposure to others
- Patients desiring pregnancy
  - Women should be counseled to wait at least 6 months after iodine-131 therapy to attempt pregnancy to avoid adverse pregnancy outcomes (such as fetal hypothyroidism, malformation, increased malignancy risk in the child, or fetal demise [with high doses]) related to RAI. For many patients a longer interval before attempting pregnancy may be recommended in order to confirm disease-free status at 6–12 months post-RAI. In these cases, earlier pregnancy is inadvisable as it would interfere with disease detection and further management.
  - In selective cases when doses are high or other considerations are present, integrating care with reproductive endocrinology/oncofertility for men and women may be appropriate.

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
EXTERNAL BEAM RADIATION THERAPY (EBRT)

General Principles

- The decision to treat and timing of treatment with EBRT for thyroid carcinoma is best made by a multidisciplinary team that must include a radiation oncologist. Evaluation by a radiation oncologist early in the course of treatment for thyroid carcinoma is preferred. The multidisciplinary team should carefully weigh the potential for benefit and the expected acute and chronic toxicity from EBRT when deciding when to incorporate EBRT into an individual patient's treatment plan.
- Consider dental, speech and swallowing, and nutrition evaluation and treatment prior to radiation therapy (RT) to determine if pre-treatment optimization of dental and oral health or gastrostomy placement is appropriate.
- Pre-treatment imaging including contrast-enhanced CT or MRI, iodine total body scan/SPECT, and FDG- or DOTATATE-PET can be used to guide radiotherapy volumes.
- For patients receiving both RAI and EBRT, the sequence of these therapies should be determined individually for each clinical circumstance.
- Conformal radiotherapy techniques including intensity-modulated RT (IMRT) with simultaneous integrated boost (SIB) and image guidance are strongly encouraged in the adjuvant/definitive setting given the potential for reduced toxicity.
- For unresected or incompletely resected anaplastic thyroid carcinoma, RT should be started as quickly as possible. Consider a rapid start with 3D RT plan converted to a more conformal RT approach when possible.
- For R0 or R1 resection of ATC, adjuvant radiotherapy or chemoradiation should start as soon as the patient is sufficiently recovered from surgery, ideally 2–3 weeks postoperatively.

Treatment Volumes

- Differentiated, Medullary or Poorly Differentiated (non-anaplastic) Thyroid Cancer – adjuvant or recurrent/persistent RT
  - Little evidence exists for appropriate treatment volumes for thyroid carcinoma. Common practice in published institutional and multi-institutional reports are described.
  - Gross residual disease in the thyroid bed or regional lymph nodes should be included in a gross tumor volume (GTV) (as defined on CT, MRI, and/or FDG-PET).
  - Clinical target volume (CTV) may include the thyroid bed (as identified on preoperative imaging, delineated by surgical clips, any residual disease/thyroid tissue). Regional lymph node levels II–VI can be included if involved or as elective volumes if not evaluated. Dose levels for each are discussed in "Dose and Fractionation" below.
  - GTV should be expanded by 0.5–1.5 cm to CTV.
  - Planning target volume (PTV) margins of 0.3–0.5 cm should be added to CTV, depending on technique and image guidance used.
- Anaplastic thyroid carcinoma[11-14]
  - GTV includes gross primary disease and involved lymph nodes (determined on contrast-enhanced CT, MRI, and/or FDG-PET, assuming obtaining these studies does not delay start of treatment).
  - High-risk CTV may include involved lymph node regions and postoperative bed in the case of partial or complete debulking surgery.
  - Elective nodal regions may be included in low-dose CTV if extended-field RT is used.
  - GTV should be expanded by 0.5–1.5 cm to CTV.
  - PTV margins of 0.3–0.5 cm should be added to CTV, depending on technique and image guidance used.

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
EXTERNAL BEAM RADIATION THERAPY (EBRT)

Dose and Fractionation

Little evidence exists for appropriate treatment volumes for thyroid carcinoma. A wide variety of dose regimens exists in the literature, and the most common practice in published institutional and multi-institutional reports are described here.[15-21] The treating radiation oncologist should use his/her clinical judgment to determine the appropriate volumes, doses, and fractionation for each patient.

Differentiated, Medullary, or Poorly Differentiated (non-anaplastic) Thyroid Cancer

- Adjuvant RT for high-risk disease (after R1 resection)
  - Microscopic disease (thyroid bed, involved resected lymph node regions): 60–66 Gy in 1.8–2 Gy per fraction
  - Elective nodal regions: 50–56 Gy in 1.6–2 Gy per fraction
- Salvage RT after R2 resection or inoperable patients
  - Gross disease: 66–70 Gy in 1.8–2 Gy per fraction
  - Microscopic disease (thyroid bed, involved resected lymph node regions): 60–66 Gy in 1.8–2 Gy per fraction
  - Elective nodal regions: 50–56 Gy in 1.6–2 Gy per fraction
- Palliative RT of metastases
  - Bony or soft-tissue metastases[22]
    - ◊ For patients with oligometastatic disease and good performance status consider higher doses (45–60 Gy) in 1.8–2 Gy daily fractions, or SBRT following principles for treatment of oligometastases
    - ◊ For patients with widely metastatic disease and/or poor performance status limiting life expectancy, consider 8 Gy in 1 fraction; 20 Gy in 5 daily fractions; 30 Gy in 10 daily fractions
  - CNS metastases
    - ◊ ≤4 metastases – consider stereotactic radiosurgery (SRS) either following surgical resection or as monotherapy
    - ◊ Multiple metastases:
      - – Consider enrollment on clinical trial for SRS versus WBRT (with or without hippocampal avoidance)
      - – Whole brain radiation – 30 Gy in 10 daily fractions; consider 45 Gy in 1.8 Gy daily fractions for good performance status[23,24]

Anaplastic Thyroid Cancer

- Adjuvant RT after R0 or R1 resection[14,25-27]
  - Microscopic disease/high-risk regions: 60–66 Gy in 1.2 Gy twice-daily fractions or 1.8–2 Gy daily fractions[26,28]
  - Elective nodal regions can be treated with SIB: 45–54 Gy in 0.8–1.0 Gy twice-daily fractions or 1.6–1.8 Gy once-daily fraction
  - Chemoradiation may be considered on an individual basis.[13]
- Salvage RT after R2 resection or inoperable patients[13,14,26]
  - Gross disease: 66–70 Gy in 1.2 Gy twice-daily fractions or 1.8–2 Gy daily fractions
  - Microscopic disease/high-risk regions: 60–66 Gy in 1.2 Gy twice-daily fractions or 1.8–2 Gy daily fractions[12,13]
  - Elective nodal regions can be treated with SIB: 45–54 Gy in 0.8–1.0 Gy twice-daily fractions or 1.6–1.8 Gy once-daily fraction
  - Chemoradiation may be considered on an individual basis.[13]
- Palliative neck RT
  - 20 Gy in 5 daily fractions, 30 Gy in 10 daily fractions, 45 Gy in 15 daily fractions
- Palliative RT of metastases
  - Bony or soft tissue metastases
    - ◊ 8 Gy in 1 fraction; 20 Gy in 5 daily fractions; 30 Gy in 10 daily fractions
  - CNS metastases
    - ◊ Whole brain radiation – 30 Gy in 10 daily fractions

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
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American Joint Committee on Cancer (AJCC)
TNM Staging For Thyroid-Differentiated and Anaplastic Carcinoma (8th ed., 2017)

Table 1. **Definitions for T, N, M**

T	Primary Tumor
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 in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension beyond the strap muscle
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

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

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American Joint Committee on Cancer (AJCC)
TNM Staging For Thyroid-Differentiated and Anaplastic Carcinoma (8th ed., 2017)

Table 2. **AJCC Prognostic Stage Groups**

Differentiated
Under 55 years

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

Differentiated
55 Years and Older

	T	N	M
Stage I	T1	N0/NX	M0
	T2	N0/NX	M0
Stage II	T1	N1	M0
	T2	N1	M0
	T3a/T3b	Any N	M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

Anaplastic

	T	N	M
Stage IVA	T1-T3a	N0/NX	M0
Stage IVB	T1-T3a	N1	M0
	T3b	Any N	M0
	T4	Any N	M0
Stage IVC	Any T	Any N	M1

Histopathologic Type

- Papillary thyroid carcinoma (PTC)
  - Papillary microcarcinoma
  - Follicular variant of PTC
  - Encapsulated variant of PTC
  - Papillary microcarcinoma
  - Columnar cell variant of PTC
  - Oncocytic variant of of PTC
- Follicular thyroid carcinoma (FTC), NOS
  - FTC, minimally invasive
  - FTC, encapsulated angioinvasive
  - FTC, widely invasive
- Hürthle cell carcinoma
- Poorly differentiated thyroid carcinoma (used for insular carcinoma as a subtype of poorly differentiated)
- Anaplastic thyroid carcinoma

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American Joint Committee on Cancer (AJCC)
TNM Staging For Thyroid-Medullary Carcinoma
(8th ed., 2017)

Table 3. **Definitions for T, N, M**

T	**Primary Tumor**
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 in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor ≥4 cm or with extrathyroidal extension
T3a	Tumor ≥4 cm in greatest dimension limited to the thyroid
T3b	Tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)
T4	Advanced disease
T4a	Moderately advanced disease; tumor of any size with gross extrathyroidal extension into the nearby tissues of the neck, including subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Very advanced disease; tumor of any size with extension toward the spine or into nearby large blood vessels, gross extrathyroidal extension invading the prevertebral fascia, or encasing the carotid artery or mediastinal vessels

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1-T3	N1a	M0
Stage IVA	T4a	Any N	M0
	T1-T3	N1b	M0
Stage IVB	T4	N0	M0
Stage IVC	Any T	Any N	M1

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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Discussion

This discussion corresponds to the NCCN Guidelines for Thyroid Carcinoma. Last updated on 12/20/2018.

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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 aged 50 years and older having palpable thyroid nodules.[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 1.2%.[7] It is estimated that approximately 53,990 new cases of thyroid carcinoma will be diagnosed in the United States in 2018.[8] As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men. Thyroid carcinoma is currently the fifth most common malignancy diagnosed in women.[8] The disease is also diagnosed more often in white North Americans than in African Americans. The main histologic types of thyroid carcinoma are: 1) differentiated (including papillary, follicular, and Hürthle cell); 2) medullary; and 3) anaplastic, which is an aggressive undifferentiated tumor. Of 63,324 patients diagnosed with thyroid carcinoma from 2011 to 2015, 89.8% had papillary carcinoma, 4.5% had follicular carcinoma, 1.8% had Hürthle cell carcinoma, 1.6% had medullary carcinoma, and 0.8% had anaplastic carcinoma.[7]

Mortality rates for thyroid carcinoma are, in general, very low. Differentiated thyroid carcinomas usually have an excellent prognosis with 10-year survival rates exceeding 90% to 95%.[9] In contrast, anaplastic thyroid carcinoma is almost uniformly lethal. However, since differentiated thyroid carcinomas represent more than 95% of all cases, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas. In 2018, it is estimated that approximately 2060 cancer deaths will occur among persons with thyroid carcinoma in the United States.[8] Thyroid carcinoma occurs more often in women; however, mortality rates are lower for younger women.[7,10-12] Although the estimated incidence of thyroid carcinoma previously increased by an average of ~5% annually between 2004 and 2013, the incidence rate has recently stabilized, likely due to more conservative indications for thyroid biopsy and the reclassification of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[8] Because overall mortality has not dramatically increased since 1975 (1150 vs. 2060 deaths), the previous increase in incidence may reflect, at least in part, earlier detection of subclinical disease (ie, small papillary carcinomas).[13-18] However, data show the incidence has increased by varying degrees across all tumor sizes and age groups.[19-28] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[29,30]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma address management for the different types of thyroid carcinoma including papillary, follicular, Hürthle cell, medullary, and anaplastic carcinoma. Additional sections in these NCCN Guidelines® include *Nodule Evaluation, Principles of Thyroid-Stimulating Hormone (TSH) Suppression, Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma,* and the AJCC staging tables.[9] This Discussion text describes the recommendations in the algorithm in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithm. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

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Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Thyroid Carcinoma, an electronic search of the PubMed database was performed to obtain key literature since the previous Guidelines update, using the following search term: thyroid carcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[31]

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

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

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma can be a challenge, because until recently, few prospective randomized trials of treatment have been done.[32,33] 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.[34] The treatment of choice is surgery, followed by radioactive iodine (RAI) ablation [iodine 131 (^{131}I)] 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.[35] 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.[36] 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 ^{131}I.[37] After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary carcinomas after being exposed to ^{131}I fallout.[38] It became evident that ^{131}I and other short-lived ^{131}Is were potent thyroid carcinogens in these children, particularly those younger than 10 years of age when they were exposed.[39] Iodine deficiency increases the risk for radiation-induced thyroid cancer.[40] Although radiation-induced papillary carcinoma tends to appear more aggressive histologically and to have high recurrence rates, the prognosis for survival is similar to that of spontaneously occurring tumors.[41-43] Iodine deficiency is associated with follicular carcinoma and anaplastic carcinomas.

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Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, Hürthle cell) 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.[1,44,45] 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 often first noticed by the patient, usually as an asymptomatic nodule.[1,44] 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.[11]

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 neck; all nodules (even incidentalomas) should have this assessment; there is no size cutoff.[3,46-48] 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).[45,49]

FNA with ultrasound guidance is the procedure of choice for evaluating suspicious thyroid nodules.[3,45,50] 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.[51-54] FNA should be considered in patients with normal or elevated TSH, certain ultrasound features, and clinical findings. FNA of clinically significant or 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 algorithm (see *Sonographic Features* in *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). Iodine 123 (^{123}I) imaging is recommended in patients with low TSH.

Sonographic (ultrasound) features can be used to predict either benign or malignant thyroid nodules. Suspicious sonographic features include hypoechoic, microcalcifications, infiltrative margins, and nodules that are taller than they are wide in the transverse plane. Ultrasound features associated with a low suspicion of malignancy include isoechoic or hyperechoic solid nodules, mixed solid/cystic nodules, or spongiform nodules without the suspicious features listed above.[47,55-57] Standardized systems for assessing ultrasound features have been created to improve consistency across centers.[56,58] 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.[57] Nonetheless, a constellation of findings—such as a nodule with internal echogenicity consistent with microcalcifications, irregular borders, and increased internal vascularity—conveys a higher risk of malignancy. Because size is a comparatively reproducible measure, its effect on likelihood of malignancy as an independent variable has been assessed. Two articles suggest that size is a relatively non-linear poor predictor of malignancy;[47,59] however, it may serve an important role in the setting of other concerning features.[60]

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

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appropriate for active surveillance rather than FNA should be based on the pattern of ultrasound features that predict benignity (eg, spongiform appearance, a pure cyst, specific intranodular appearances) or small size due to treatment considerations as previously noted.[55,56,61] 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 (eg, hypoechoic, rounded, absent of fatty hilum, cystic or partially cystic, microcalcifications) 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.[16,62] 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).[4,13,47,63-67] In selected cases, it may be reasonable to follow these nodules with serial ultrasounds. 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.[68] These observations cast doubt on the clinical benefit of diagnosing (and treating) papillary microcarcinoma in these selected groups.[69] Others feel that surgery should be considered for select patients with papillary carcinomas who are 45 years of age or older.[70]

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).[3,49,71] The NCCN recommendations describe which nodules require further assessment with FNA and which can undergo active surveillance. In 2015, the ATA updated its guidelines on the management of thyroid nodules and thyroid cancer; its comprehensive guidelines also discuss ultrasound and FNA.[72] 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).[45,49] The Society of Radiologists in Ultrasound wrote a consensus statement in 2005 about management of thyroid nodules identified at thyroid ultrasonography. Its 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.[71] 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).[73,74] 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 symptoms of invasion into neck structures are present.[74,75] 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.[75] 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

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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 carcinoma 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.[3,76]

Some clinicians, especially in Europe,[77] recommend obtaining serum calcitonin levels from all patients with thyroid nodules to assess for medullary carcinoma. 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 to screen all patients with thyroid nodules for medullary carcinoma.[3] A study showed that calcitonin screening may be cost effective in the United States.[78] 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.[79]

FNA Results

Cytologic examination of an FNA specimen is typically categorized as: category I: nondiagnostic or unsatisfactory biopsy; category II: benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis); category III: atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); category IV: follicular neoplasm or suspicious for follicular neoplasm (includes Hürthle cell neoplasm); category V: suspicious for malignancy; or category VI: malignancy (includes papillary, medullary, anaplastic, or lymphoma). These diagnostic categories for FNA results reflect the 2017 Bethesda System for Reporting Thyroid Cytopathology.[80] 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 papillary carcinoma—false-negative results are sometimes obtained; therefore, a reassuring FNA should not override worrisome clinical or radiographic findings.[81,82]

Molecular diagnostic testing to detect individual mutations (eg, *BRAF* V600E, *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.[83-91] The *BRAF* V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation.[92] Some studies have linked the *BRAF* V600E mutation to poor prognosis, especially when occurring with *TERT* promoter mutation.[93-96] The choice of the precise molecular test depends on the cytology and the clinical question being asked.[97-100] Indeterminate groups include: 1) follicular or Hürthle cell neoplasms; and 2) AUS/FLUS.[101-103] The NCCN Panel recommends molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[104,105]

Historically, studies have shown that molecular diagnostics do not perform well for Hürthle cell neoplasms.[102,106,107] A 2015 publication of 134 patients looked at the performance of the Afirma gene expression classifier (GEC) in guiding management of FNA diagnoses of suspicious for Hürthle cell neoplasm or AUS concerning for Hürthle cell neoplasm. This study found that 86% of patients with suspicious findings on Afirma GEC had unnecessary surgery.[107] However, results that were presented at the ATA

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2017 Annual Meeting described improved results using the Afirma Genomic Sequencing Classifier (GSC) with two dedicated classifiers to 1) differentiate Hürthle cell-containing specimens from non-Hürthle specimens and 2) differentiate neoplastic Hürthle specimens from non-neoplastic. By applying this process to 186 specimens, this study reported an 88.9% sensitivity for detection of Hürthle cell malignancies and a 58.8% specificity for identification of benign Hürthle lesions, representing a marked improvement over previous results.[108] Another molecular test, the ThyroSeq v3 Genomic Classifier, has also shown promise for diagnosis of Hürthle cell-containing specimens. This test analyzes 112 genes for a variety of genetic alterations and was validated in 238 tissue samples and 174 FNA samples with known surgical follow-up. A 2018 publication on the ThyroSeq v3 Genomic Classifier reported a sensitivity of 92.9% (95% CI, 80.52%–98.50%) and a specificity of 69.3% (95% CI, 48.21%–85.67%) for detecting Hürthle cell cancers.[109]

Molecular diagnostic testing may include multigene assays (eg, the GEC) or individual mutational analysis. The GEC measures the expression of at least 140 genes.[84,110,111] In addition to their utility in diagnostics, molecular markers may drive decisions related to targeted therapy for advanced disease and inform eligibility for some clinical trials. In addition, the presence of some mutations may have prognostic importance.

A minority of panelists expressed concern regarding active surveillance 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 recommendations for either active surveillance or considering lobectomy in lesions classified as benign by molecular testing). Clinical risk factors, sonographic patterns, and patient preference can help determine whether active surveillance or lobectomy is appropriate for these patients (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 active surveillance if the application of a specific molecular diagnostic test (in conjunction with clinical and ultrasound features) 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 from FNA can vary widely between institutions.[80,112] 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.[105,113]

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of medullary carcinoma.[49] Hürthle cell neoplasms can sometimes mimic medullary carcinoma cytologically and on frozen section. Sometimes it can be difficult to discriminate between anaplastic carcinoma and other primary thyroid malignancies (ie, medullary carcinoma, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[114] Metastatic renal carcinoma can mimic follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma.[49] Pathology synoptic reports (protocols), such as those from the College of American Pathologists (CAP), are useful for reporting results from examinations of surgical specimens. The CAP protocol was updated in June 2017 and reflects the 8th edition AJCC Staging Manual (see *Protocol for the Examination of*

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Specimens From Patients With Carcinomas of the Thyroid Gland on the CAP website).[9,115]

Follicular and Hürthle cell carcinomas are rarely diagnosed by FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.[34,45,81,116] Approximately 15% to 40% of lesions classified as "follicular neoplasm" or "suspicious for follicular neoplasm" are malignant, with risk of malignancy varying by institution, cytopathologist, and whether or not NIFTP is excluded.[117,118] 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.[119] Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful for follicular cell carcinomas (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[73,105,120]

In some patients with follicular lesions, serum TSH level and thyroid ^{123}I 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.[3,121] 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 hypofunctional (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 an increased 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).[74] In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.[122] Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of significant growth.[74] Significant nodule growth is defined as a greater than 50% increase in nodule volume or 20% increase in size of 2 to 3 dimensions.[123] Size changes should be greater than 2 mm and assessed by direct comparison of images. 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.[11] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[124,125] 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.[11] Distant metastases were the sites of recurrence in 21% of patients in this cohort, most often

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(63%) in the lungs alone. Of the patients with distant metastases, 50% died of cancer.[11]

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.[3,126] 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 with an increase in mortality.[127,128]

Prognosis

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular carcinomas, patient age at the time of initial therapy and tumor stage are important.[11,129-131] 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 of age, 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.[11,129-132] 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.[133,134] 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.[135] 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.[136-138] 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.[11,133,139,140] Prognosis is less favorable in men than in women, but the difference is usually small.[11,138] 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.[11] Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.[141]

Familial Syndromes

Familial, non-medullary carcinoma accounts for about 5% of papillary thyroid carcinomas (PTCs) and, in some cases, may be clinically more aggressive than the sporadic form.[142,143] For patients to be considered as having familial papillary carcinoma, most studies require at least 3 first-degree relatives to be diagnosed with papillary carcinoma because the finding of cancer in a single first-degree relative may just be a chance event. Microscopic familial papillary carcinoma tends to be multifocal and bilateral, often with vascular invasion, lymph node metastases, and high rates of recurrence and distant metastases.[144] Other familial syndromes associated with papillary carcinoma are familial adenomatous polyposis,[145]

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Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands),[146] and Cowden syndrome (multiple hamartomas).[147] The prognosis for patients with all of these syndromes is not different from the prognosis of those with spontaneously occurring papillary carcinoma.

Tumor Variables Affecting Prognosis

Some tumor features have a profound influence on prognosis.[132,148-150] The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, *BRAF* V600E mutation status, and metastases.[93,94,151] For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.[3,152-155] The CAP protocol provides definitions of vascular invasion and other terms (see *Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland* on the CAP website).[115] In patients with sporadic medullary carcinoma, a somatic RET oncogene mutation confers an adverse prognosis.[156]

Histology

Although survival rates with typical papillary carcinoma 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.[34,157,158]

NIFTP, formerly known as noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), is characterized by its follicular growth pattern, encapsulation or clear demarcation of the tumor from adjacent tissue with no invasion, and nuclear features of papillary carcinoma.[159,160] NIFTP tumors have a low risk for adverse outcomes and, therefore, require less aggressive treatment.[160-163] NIFTP was re-classified in 2016 to prevent overtreatment of this indolent tumor type as well as the psychological consequences of a cancer diagnosis on the patient.[159,160] CAP updated its protocols with NIFTP in the June 2017 version.[115]

While molecular diagnostic testing may be useful for diagnosing NIFTP in the future, currently available tests were not validated using NIFTP samples. Studies have shown that NIFTP specimens frequently carry characteristic mutations/alterations including *RAS*, *PAX8/PPARγ*, and/or *BRAF* (with the exception of the aggressive *BRAF* V600 mutations), differentiating it from papillary subtypes that more frequently show *BRAF* V600E and *RET/PTC* alterations.[87,164,165] However, multiple studies investigating the performance of molecular diagnostics for this subtype have reported that most thyroid nodules histologically diagnosed as NIFTP are classified as "suspicious" by GEC, possibly leading to more aggressive surgical treatment than is necessary.[166,167] Therefore, the validation of molecular diagnostics with NIFTP samples will be necessary to ensure that the tests are accurately classifying these.

Follicular thyroid carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. 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.[168] 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.[169] FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.[45,116] Therefore, the tumor is often simply referred to as a "follicular neoplasm" by the cytopathologist (see *Nodule Evaluation* in the

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NCCN Guidelines for Thyroid Carcinoma).[81] The diagnosis of follicular thyroid carcinoma is assigned only after analysis of the permanent histologic sections—obtained from diagnostic lobectomy or thyroidectomy—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.[132] The poor prognosis is closely related to older age at the time of diagnosis, advanced tumor stage, and larger tumor size.[11] 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.[11,170]

When Hürthle (oncocytic) cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as Hürthle cell carcinoma. Previously considered a variant of follicular thyroid carcinoma, the World Health Organization (WHO) and AJCC reclassified Hürthle cell carcinoma as a separate entity in 2017.[9,171] Molecular studies suggest that this tumor may be more similar to papillary than to follicular thyroid carcinomas[172,173] and genotyping revealed that mutational, transcriptional, and copy number profiles of Hürthle cell carcinomas were distinct from papillary and follicular carcinomas, best categorizing it as a unique class of thyroid malignancy.[174] Benign and malignant Hürthle cell 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.[175] 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.[176,177] 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.[178-180] In contrast to papillary or follicular carcinomas, ^{131}I may be not effective in patients with Hürthle cell carcinoma because fewer Hürthle cell carcinomas concentrate ^{131}I. In a series of 100 patients with distant metastases, ^{131}I 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.[178] In the National Cancer Database report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.[181]

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.[182] 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.[183,184] 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,[185] which may be the presenting feature and also may be associated with distant metastases.[182] 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; the 30-year cancer-specific mortality

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is 0.4% compared to 7% ($P < .001$) for tumors 1.5 cm or larger.[11] In fact, the prognosis for papillary and follicular thyroid carcinomas is incrementally poorer as tumors increase in size.[170,186] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas.[11]

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 carcinomas.[11,187] 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.[11,188]

Lymph Node Metastases

In one review, nodal metastases were found in 36% of 8029 adults with papillary carcinoma, in 17% of 1540 patients with follicular thyroid carcinoma, and in up to 80% of children with papillary carcinoma.[132] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[189] 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).[190] Older patients (>45 years) with papillary carcinoma and lymph node metastases also have decreased survival.[191] A 2012 review by Randolph et al emphasized the correlation between the size and number of metastatic lymph nodes and the risk of recurrence.[192] 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 carcinomas.[193,194] About 50% of these metastases are present at the time of diagnosis.[132] Distant metastases occur even more often in patients with Hürthle cell carcinoma (35%) and in those patients who are older than age 40 years at diagnosis.[178,179] Among ^{123}1 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, and whether the metastases concentrate ^{131}I.[178,179,195,196]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[132] Even so, some pulmonary metastases are compatible with long-term survival.[197] 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.[198] The survival rates are highest in young patients with diffuse lung metastases seen only on ^{131}I imaging and not on x-ray.[196,198,199] Prognosis is worse with large pulmonary metastases that do not concentrate ^{131}I.[178,179,195]

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, many clinicians place a stronger

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emphasis on potential morbidity than on mortality (see *Surgical Complications* in this Discussion). The current 2017 AJCC staging guidelines (8th edition) for thyroid carcinoma may be useful for prognosis (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma).[9] Many studies (including those described in this Discussion) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[200] and not the 6th, 7th, or 8th editions.[9,201,202]

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.[130,136,201-203] 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.[186] 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.[136]

Unfortunately, a study that classified 269 patients with papillary carcinoma according to 5 different prognostic paradigms found that some patients in the lowest-risk group from each approach died of cancer.[139] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[201,204] The AJCC TNM staging approach (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 55 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,[205,206] 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.[130,207]

A three-tiered staging system—low, intermediate, high—that uses clinicopathologic features to risk stratify with regard to the risk of recurrence has been suggested and validated.[3,208-211] 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. In another approach, 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.[212] 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 papillary carcinoma, 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.[213] Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring[138] and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic Cancer Center for low-risk PTCs (MACIS score ≤3.99) had no improvement in survival rates after undergoing procedures more

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extensive than ipsilateral lobectomy. Thus, the authors concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[214]

Cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy were assessed in patients with papillary carcinoma considered to be low risk by AMES criteria.[215] 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 papillary carcinoma.[215]

Most NCCN Panel Members recommend total thyroidectomy for patients with biopsy-proven papillary carcinoma who have large-volume pathologic N1 metastases (>5 involved nodes with metastases >2 mm in largest dimension),[3,34,216] because this procedure is associated with improved disease-free survival.[124,140,215,217] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.[132,214] After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and ^{131}I therapy)[11] and the highest frequency (11%) of subsequent pulmonary metastases.[218] However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.[41] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.[11]

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 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.[137,203,219] The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole-body ^{131}I imaging. Panel members recommend total lobectomy (without radioactive iodine RAI ablation) for patients with papillary carcinoma who have small-volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm, in largest dimension).[220]

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).[3,11,182,221-224] Total lobectomy alone is also adequate treatment for NIFTP pathologies (see *Tumor Variables Affecting Prognosis, Histology*) and 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 resection 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.[151,225,226]

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

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without) whole-body ^{131}I imaging. Large thyroid remnants are difficult to ablate with ^{131}I.[218] 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.[187,227-233] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[230]

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.[140] 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.[231]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy.[213] Transient clinical hypoparathyroidism after surgery is common in adults[234] and children[140,235] 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.[236] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[237] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[238] 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.[239]

Radioactive Iodine—Diagnostics and Treatment

Diagnostic Total Body Imaging and Thyroid Stunning

When indicated, diagnostic total body ^{131}I imaging is recommended (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 ^{131}I induce follicular cell damage.[240] Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent ^{131}I.[241]

To avoid or reduce the stunning effect, the following have been suggested: 1) the use of ^{123}I or small (2 or 3 mCi) doses of ^{131}I; and/or 2) a shortened interval (≤72 hours) between the diagnostic ^{131}I dose and the therapy dose. However, ^{123}I is more expensive and smaller ^{131}I doses have reduced sensitivity when compared with larger ^{131}I doses.[240-242] In addition, a large thyroid remnant may obscure detection of residual disease with ^{131}I imaging. Some experts recommend that diagnostic ^{131}I imaging be avoided completely with decisions based on the combination of tumor stage and serum Tg.[240] Other experts advocate that whole-body ^{131}I 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.[3,240,243-245] Thus, NCCN Panel Members disagreed about using diagnostic total body ^{131}I imaging before postoperative RAI, which is reflected in the category 2B recommendation

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for imaging.[3,246-248] Note that diagnostic imaging is used less often for patients at low risk.

Eligibility for Postoperative Radioactive Iodine (RAI)

The NCCN Panel recommends a selective use approach to postoperative RAI administration. 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. The NCCN Guidelines have 3 different pathways for postoperative RAI administration based on clinicopathologic factors: 1) RAI typically recommended; 2) RAI selectively recommended; and 3) RAI not typically recommended (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).

Postoperative RAI is typically recommended for patients at high risk of having persistent disease remaining after total thyroidectomy and includes patients with any of the following factors: 1) gross extrathyroidal extension; 2) a primary tumor greater than 4 cm; or 3) postoperative unstimulated Tg greater than 5 to 10 ng/mL. In the case of follicular or Hürthle cell carcinoma, extensive vascular invasion is another indication for postoperative RAI. Postoperative RAI is also frequently recommended for patients with known/suspected distant metastases at presentation (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).

Postoperative RAI is selectively recommended for patients who are at greater risk for recurrence with any of the following clinical indications such as largest primary tumor 2 to 4 cm, high-risk histology (for papillary carcinoma), lymphatic or vascular invasion, cervical lymph node metastases, macroscopic multifocality (one focus >1 cm), unstimulated postoperative serum Tg (<5–10 ng/mL), or microscopic positive margins.[3,249,250] However, the NCCN Panel does not routinely recommend RAI for patients with all of the following factors: 1) either unifocal (<2 cm) or multifocal classic papillary microcarcinomas (all foci ≤1 cm) confined to the thyroid; 2) no detectable anti-Tg antibodies; and 3) postoperative unstimulated Tg less than 1 ng/mL. 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.[3,251]

Postoperative Administration of RAI

Studies show decreased recurrence and disease-specific mortality for populations at intermediate or higher risk when postoperative ^{131}I therapy is administered as part of the initial treatment.[11,131,139,252-254] 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 ^{131}I ($P < .001$). Moreover, fewer patients developed distant metastases ($P < .002$) after thyroid remnant ^{131}I 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.[252] Another study of 21,870 intermediate risk patients with differentiated thyroid cancer found that postoperative RAI improved OS ($P < .001$) and was associated with a 29% reduction in the risk of death after adjustment for demographic and clinical factors (HR, 0.71; 95% CI, 0.62–0.82; $P < .001$).[254] Some studies have found that remnant ablation had less of a therapeutic effect, perhaps because more extensive locoregional surgery had been done.[186]

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.[255] Longer follow-up suggests that overall survival is not decreased or increased in these patients.[256] However, a more recent study reported that the incidence of

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secondary malignancies, such as leukemia and salivary gland malignancies, has increased in patients with low-risk thyroid cancer (ie, T1N0) who received RAI.[257] Debate continues about ablating the thyroid bed with ^{131}I after total thyroidectomy.[3,186,252,258] In patients with papillary carcinoma who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates.[224,250,259] A long-term study (n = 1298) found that overall survival is not improved in patients who receive RAI ablation.[260] 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, which 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.

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).[32,33] The NCCN Guidelines reflect a more cautious approach to using RAI ablation based on these randomized trials.[261] If RAI ablation is used, the NCCN Guidelines recommend (category 1) 30 mCi of ^{131}I 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).[262] RAI ablation is not recommended in patients at very low risk.

RAI therapy for thyroid cancer carries the risk of possible adverse effects including salivary gland dysfunction, lacrimal gland dysfunction, transient gonadal dysfunction, and secondary primary malignancies.[263] The possible benefits of RAI should be weighed with the risk of adverse effects as part of treatment decision-making.[261] Adverse effects may be minimized by using lower doses of RAI.[32]

Historically, the 3 methods of determining ^{131}I therapy activities (doses) have included: empiric fixed doses, quantitative dosimetry, and upper-bound limits that are set by blood dosimetry.[3,240,243,264,265] Most patients at NCCN Member Institutions receive postoperative RAI 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 ^{131}I 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 ^{131}I doses in patients who are ambulatory.[264] However, ^{131}I therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses.

Administration of a fixed dose of ^{131}I is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of ^{131}I in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of ^{131}I. Lymph node metastases may be treated with about 100 to 175 mCi (3700–6475 MBq) of ^{131}I. Cancer growing through the thyroid capsule (and incompletely resected) is treated with 150 to 200 mCi (5550–7400 MBq). Patients with distant metastases are usually treated with 100 to 200 mCi (3700–7400 MBq) of ^{131}I, 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.[266,267] Diffuse pulmonary metastases that concentrate 50% or

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more of the diagnostic dose of ^{131}I (which is very uncommon) are treated with 150 mCi of ^{131}I (5550 MBq) or less to avoid lung injury, which may occur when more than 80 mCi remains in the whole body 48 hours after treatment. The administered activity of RAI therapy should be adjusted for pediatric patients.[3,268-270] A 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.[271]

Post-Treatment ^{131}I Imaging

When ^{131}I therapy is given, whole-body ^{131}I imaging should be performed several days later to document ^{131}I uptake by the tumor. Post-treatment whole-body ^{131}I 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.[264] 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.[272] Post-treatment imaging was most likely to reveal clinically important new information in patients younger than 45 years who had received ^{131}I therapy in the past. Conversely, in older patients and patients who had not previously received ^{131}I therapy, post-treatment imaging rarely yielded new information that altered the patient's prognosis.[272]

Assessment and Management After Initial Treatment

Serum Tg determinations, neck ultrasound, and whole-body ^{131}I imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation.[273] In contrast, neither serum Tg nor whole-body ^{131}I 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.[274,275]

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.[276] 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) ^{131}I 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 ^{131}I uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.[277] Administration of rhTSH is well tolerated; nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[275] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[277]

An international study was performed to assess the effects of 2 rhTSH dosing schedules on whole-body ^{131}I imaging and serum Tg levels when

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compared with imaging and Tg levels obtained after thyroid hormone withdrawal.[275] Data showed that the combination of rhTSH–stimulated whole-body imaging and serum Tg measurements detected 100% of metastatic carcinoma.[275] In this study, 0.9 mg of rhTSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of ^{131}I on the third day. Whole-body imaging and Tg measurements were performed on the fifth day. Whole-body ^{131}I 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.[275,278]

Measuring Serum Tg and Anti-Tg Antibodies

Serum Tg measurement is the best means of detecting thyroid tissue, including carcinoma. Tg can 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 ^{131}I imaging.[274-276,279] Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or rhTSH stimulation. Serum Tg generally does not increase as much after rhTSH administration as after withdrawal of thyroid hormone. The conditions for rhTSH–stimulated, whole-body ^{131}I imaging stipulate using 4-mCi ^{131}I doses (based on the trial)[275] and an imaging time of 30 minutes or until 140,000 counts are obtained. Tg measurements may also be obtained without stimulating TSH using ultrasensitive assays (ie, second-generation Tg immunometric assays [TgIMAs]).[280,281] It is useful to measure serum Tg and anti-Tg antibody levels for follow-up and assessing trend patterns.

The sensitivity and specificity of various Tg assays, however, vary widely in different laboratories, even with the use of an international standard (CRM 457).[282,283] 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 may 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.[280,283,284] These antibodies typically falsely lower the Tg value in immunochemiluminometric assays (ICMAs) and immunoradiometric assays (IRMAs), while raising the value in older radioimmunoassays. 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.[284]

In one study, 49% of patients had a recurrence if they had undetectable serum Tg and serum anti-Tg antibody levels of 100 units/mL or more when compared with only 3% of patients with undetectable serum Tg and serum anti-Tg antibodies of less than 100 units/mL.[285] In patients with coexistent autoimmune thyroid disease at the time of surgery, anti-Tg antibodies may persist for 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.[286] Patients with persistently undetectable serum Tg and anti-Tg antibody levels have longer disease-free survival when compared with patients who have detectable levels.[287]

Treating Patients with Positive Tg and Negative Imaging

Post-treatment ^{131}I 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 ^{131}I imaging, neck ultrasonography, CT, MRI, or PET.

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Pulmonary metastases may be found only after administering therapeutic doses of ^{131}I and obtaining whole-body imaging within a few days of treatment.[288] In a study of 283 patients treated with 100 mCi (3700 MBq) of ^{131}I, 6.4% had lung and bone metastases detected after treatment that had been suspected based on high serum Tg concentrations alone but that had not been detected after 2-mCi (74 MBq) diagnostic imaging.[289]

Unfortunately, most patients who are diagnostic imaging–negative and Tg-positive are not rendered disease free by ^{131}I therapy; however, the tumor burden may be diminished.[290] 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 ^{131}I is very low; thus, the tumor will not respond to ^{131}I therapy.

Thyroid Hormone Suppression of TSH

The use of postoperative 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.[3,243,291,292] 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 milliunits/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 lower limit of 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.[3,293] An adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d) is recommended for patients whose TSH levels are chronically suppressed. However, reports do not suggest that bone mineral density is altered in patients receiving levothyroxine.[294,295]

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated with thyroid hormone suppressive therapy.[11,252,255,292,296-298] 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).[298] 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.[255] 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).[299-301] One retrospective study reported a benefit of adjuvant EBRT after RAI in patients older than 40 years of age with invasive papillary carcinoma (T4) and lymph node

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involvement (N1).[302] 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 papillary carcinoma with microscopic residuum. Not all patients received RAI therapy.[131] Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of papillary carcinoma. 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%).[303]

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%).[303] However, these patients had not received RAI. Similar benefit was shown with RAI alone in comparable patients treated with RAI after surgery.[303] 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.[304] Other data from single institutions also show that adjuvant EBRT yields long-term control of locoregional disease.[305-307] Studies suggest that intensity-modulated radiation therapy (IMRT) is safe, effective, and less morbid in patients with thyroid cancer.[305,308]

External-Beam RT and Surgical Excision of Metastases

Surgical excision, EBRT, stereotactic body radiation therapy (SBRT), or other local therapies can be considered for symptomatic isolated skeletal metastases or those that are asymptomatic in weight-bearing sites.[309,310] Brain metastases pose a special problem, because ^{131}I 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.[311,312] 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.[313] Most recurrent tumors respond well to surgery; ^{131}I therapy; EBRT, SBRT, or IMRT; or other local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA).[3,314]

Systemic Therapy

Systemic therapy can be considered for tumors that are not surgically resectable; are not responsive to ^{131}I; are not amenable to EBRT treatment, SBRT, IMRT, or other local therapies; 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.[315] In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.[316] Combination chemotherapy is not clearly superior to doxorubicin therapy alone.[132] Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease.[317] Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.[318-325] Agents include multitargeted kinase inhibitors, such as lenvatinib,[318,321,326-332] sorafenib,[333-340] sunitinib,[338,341,342] axitinib,[343-345] everolimus,[346,347] vandetanib,[348] cabozantinib,[319,349] and pazopanib;[350] BRAF V600E mutant inhibitors, such as vemurafenib and dabrafenib;[351-354] and tropomyosin receptor kinase (TRK) inhibitors, such as larotrectinib.[355] Data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in patients with papillary carcinoma who have ALK gene fusion.[356-359]

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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.[321,329,338,350,360-362] Lenvatinib and sorafenib are recommended for the treatment of patients with RAI-refractory differentiated thyroid cancer (see *Papillary Thyroid Carcinoma* in this Discussion and the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Vandetanib and cabozantinib, oral kinase inhibitors, are recommended for the treatment of medullary carcinoma in patients with unresectable locally advanced or metastatic disease (see *Medullary Thyroid Carcinoma* in this Discussion and the NCCN Guidelines for Medullary [Thyroid] Carcinoma). 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.[328,329,363-368] Dose modifications of kinase inhibitors may be required. Pazopanib has been reported to cause reversible hypopigmentation.[369]

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.[370] 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.[371] Surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients.[372] In more than 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects.[373] Preoperative ultrasound findings altered the operation in more than 40% of cases. In another report,[374] 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, particularly if cytology is negative. 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, although iodinated contrast will delay treatment with RAI. Evaluation of vocal cord mobility may be considered for patients with abnormal voice, a surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Vocal cord mobility may be evaluated by ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy.[375]

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).[3,376,377] A total thyroidectomy is recommended for patients with any one of the following factors, including: known distant metastases, extrathyroidal extension, tumor greater than 4 cm in diameter, cervical lymph node metastases, or poorly differentiated histology. Total thyroidectomy may be considered for patients with bilateral nodularity or a prior exposure to radiation (category 2B for radiation exposure). 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.[378] Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Based on the results of a randomized

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controlled trial, the panel does not recommend prophylactic central neck dissection if the cervical lymph nodes are clinically negative. This trial of 181 patients with PTC randomized patients to receive either total thyroidectomy alone or total thyroidectomy plus central neck dissection and showed no difference in outcomes between the two groups.[379] 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 with PTC who are assumed to be at lower risk of cancer-specific mortality. As previously mentioned, the 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 *Ipsilateral Lobectomy Versus Total Thyroidectomy* in this Discussion). Lobectomy plus isthmusectomy is recommended for patients who cannot (or refuse to) take thyroid hormone replacement therapy for the remainder of their lives.[213] 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 therapy.

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.[380] 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.[381] However, most guidelines (eg, NCCN, ATA) do not recommend active surveillance for patients with PTC.[3] Another study of 2784 patients with differentiated thyroid carcinoma (86% with PTC) found that total thyroidectomy was associated with increased survival in patients at high risk.[255] 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.[382] 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 resection margins, gross extrathyroidal extension, macroscopic multifocal disease, vascular invasion, or macroscopic nodal metastases. While a retrospective study using the National Cancer Database has shown that a sizable percentage of patients with differentiated thyroid cancer receive RAI therapy following lobectomy,[383] the panel does not support this practice due to a lack of data showing benefit. Therefore, RAI is not recommended following lobectomy for differentiated thyroid cancer.

Incidentally discovered PTCs 1 to 4 cm in size may warrant a completion thyroidectomy (category 2B) for lymphatic invasion (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma); active surveillance (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 low or normal TSH levels (see *Principles of TSH Suppression* in the NCCN Guidelines for Thyroid Carcinoma). Lobectomy is sufficient for tumors resected with all of the following: negative resection 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).

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Radioactive Iodine Therapy

Postoperative RAI administration is recommended when a number of clinical factors predict a significant risk of recurrence, distant metastases, or disease-specific mortality. Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Algorithms can 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 is not recommended after lobectomy; 3) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 4) RAI is often used for patients with known or suspected distant metastatic disease at presentation. However, some patients may have metastatic disease that may not be amenable to RAI therapy, which is also known as iodine-refractory disease (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).

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.[270] For patients with unresectable gross residual disease in the neck (suspected or proven) that is refractory to RAI, EBRT or IMRT can be considered if disease is threatening vital structures (see *Postsurgical Evaluation* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,305,306,384-386]

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] About 85% of patients are considered to be low risk after surgery for papillary thyroid cancer.[3] In patients who have had total (or near total) thyroidectomy and thyroid remnant ablation, the ATA Guidelines define the absence of persistent tumor (also known as no evidence of disease [NED]) as: 1) absence of clinical evidence of tumor; 2) absence of imaging evidence of tumor; and 3) undetectable Tg levels (during either TSH suppression or TSH stimulation) and absence of anti-Tg antibodies.[3] Patients treated with ^{131}I 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] Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.[3]

RAI imaging (TSH-stimulated [during either TSH suppression or TSH stimulation]) can be considered in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality; patients with previous RAI-avid metastases; or patients with abnormal Tg levels, stable or increasing anti-Tg antibodies, or abnormal ultrasound results. In patients selected for monitoring with RAI imaging it is recommended every 12 to 24 months until no clinically significant response is seen to RAI treatment in patients with iodine-responsive tumors and detectable Tg, distant metastases, or soft tissue invasion on initial staging. Non-RAI imaging—such as ultrasound of the central and lateral neck compartments, neck CT, chest CT, or FDG-PET/CT—may be

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considered if RAI imaging is negative and stimulated Tg is greater than 2 to 5 ng/mL. High-risk factors include incomplete tumor resection, macroscopic tumor invasion, and distant metastases in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality (see *Consideration for Initial Postoperative RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3]

Recurrent 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.[3] Cross-sectional imaging with CT or MRI may also be valuable for evaluation and surgical planning, 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, particularly if cytology is negative.

Clinically significant nodal recurrence in a previously undissected nodal basin should be treated with a formal compartmental resection.[3] 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 Guidelines for Thyroid Carcinoma. 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 recurrence, RAI treatment and EBRT or IMRT are recommended if the ^{131}I imaging is positive.[296,372] Local therapies, such as ethanol ablation or RFA, are also an option if available. EBRT or IMRT alone is another option in the absence of ^{131}I uptake for select patients not responsive to other therapies.[306,387] 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 using an empiric fixed dose of 100 to 150 mCi of ^{131}I (see *Recurrent Disease* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). The NCCN Panel had a major disagreement about recommending (category 3) post-treatment ^{131}I imaging in this setting, because some do not feel that these patients should have imaging. No study has shown a decrease in morbidity or mortality in patients treated with ^{131}I 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.[388] 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.[389,390] Active surveillance may be considered for patients with low-volume disease that is stable and distant from critical structures.

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Metastatic Disease Not Amenable to RAI Therapy

For metastatic disease not amenable to RAI therapy, several therapeutic approaches are recommended, depending on the site and number of tumor foci (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,391] 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 EBRT, SBRT, or other local therapies.[309,310,392-394] 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.[395-397] Embolization (or other interventional procedures) of metastases can also be considered either prior to resection or as an alternative to resection.[392,398]

For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred (see the NCCN Guidelines for Central Nervous System Cancers).[311,312] For multiple CNS lesions, surgical resection and/or EBRT can be considered (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).

For clinically progressive or symptomatic disease, recommended treatment options that could be considered include: 1) lenvatinib (preferred) or sorafenib;[328,333] 2) clinical trials; 3) other small molecule kinase inhibitors if a clinical trial is not available; or 4) resection of distant metastases and/or EBRT or IMRT.[399,400] The recommendations for lenvatinib (preferred) or sorafenib are based on phase 3 randomized trials.[328,333] The NCCN Panel feels that lenvatinib is the preferred agent in this setting based on a response rate of 65% for lenvatinib when compared with 12% for sorafenib, although these agents have not been directly compared.[326,328,333] The decision to use lenvatinib or sorafenib should be individualized for each patient based on likelihood of response and comorbidities. The efficacy of lenvatinib or sorafenib for patients with brain metastases has not been established; therefore, consultation with neurosurgeons and radiation oncologists is recommended. Kinase inhibitors have been used as second-line therapy for thyroid cancer.[329,330]

Lenvatinib was compared with placebo in patients with metastatic differentiated thyroid cancer that was refractory to RAI in a phase 3 randomized trial.[328] Patients receiving lenvatinib had a progression-free survival (PFS) of 18.3 months compared with 3.6 months for those receiving placebo (hazard ratio [HR], 0.21; 99% CI, 0.14–0.31; $P < .001$). Six treatment-related deaths occurred in the lenvatinib group. A prespecified subset analysis of this trial found that the PFS benefit of lenvatinib compared to placebo was maintained in both older (>65 years) and younger (≤65 years) patients. Furthermore, a longer median overall survival was observed in older patients treated with lenvatinib compared to placebo (HR, 0.27; 95% CI, 0.31–0.91; $P = .20$), although older patients also had higher rates of grade 3 and higher adverse effects from treatment. These results suggest that lenvatinib is an appropriate treatment option for patients of any age with RAI-refractory differentiated thyroid cancer.[401]

Another phase 3 randomized trial compared sorafenib with placebo in patients with RAI-refractory metastatic differentiated thyroid cancer.[333] Patients receiving sorafenib had a PFS of 10.8 months compared with 5.8 months for those receiving placebo (HR, 0.59; 95% CI, 0.45–0.76; $P < .0001$). One treatment-related death occurred in the sorafenib group. Hand-foot syndrome is common with sorafenib and may require dose adjustments.

Other commercially available small-molecule kinase inhibitors may also be considered for progressive and/or symptomatic disease if a clinical trial is not available—including vemurafenib or dabrafenib (for *BRAF*-positive

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disease), larotrectinib (for *NTRK* gene fusion positive disease), axitinib, everolimus, pazopanib, sunitinib, vandetanib, or cabozantinib—although some of these have not been approved by the FDA for differentiated thyroid cancer (see *Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma* in the NCCN Guidelines for Thyroid Carcinoma). Note that kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.[328,333,364,402,403] Active surveillance is often appropriate for asymptomatic patients with indolent disease and no brain metastasis.[329,364]

Follicular Thyroid Carcinoma

The diagnosis and treatment of papillary and follicular thyroid carcinoma are similar; therefore, 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.[45,404] Unlike PTC, FNA is not specific for follicular thyroid carcinoma and accounts for the main differences in management of the 2 tumor types.[74,81,116,405] 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. Molecular diagnostic testing may be useful to determine the status of follicular lesions or lesions of indeterminate significance (including follicular neoplasms, AUS, or FLUS) as more or less likely to be malignant based on the genetic profile. 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.[404,406] 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 few (1-4) foci of vascular invasion and often requires examination of at least 10 histologic sections.[407] Minimally invasive cancers, as well as NIFTP tumors, may also be simply followed carefully, because minimally invasive follicular carcinomas and NIFTP 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 PTC. Clinicopathologic factors can be used to guide decisions about whether to administer initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). The NCCN Guidelines provide algorithms 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

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known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

RAI ablation may be used to destroy residual thyroid tissue for suspected or proven thyroid bed uptake; alternatively, patients fitting these criteria may be followed without RAI ablation. Iodine 131 ablation and post-treatment imaging (with consideration of dosimetry for distant metastasis) are recommended for suspected or proven ^{131}I-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 ^{131}I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before ^{131}I therapy is administered is a category 2B recommendation for both follicular thyroid carcinoma 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,[202,408] although the prognosis of Hürthle cell carcinoma is worse.[177,404,406,409,410] Molecular diagnostic testing may not perform well for Hürthle cell neoplasm as discussed in *FNA Results*, above. The Hürthle cell variant of PTC is rare and seems to have a prognosis similar to follicular carcinoma.[411]

The management of Hürthle cell 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 ^{131}I (see *Papillary Thyroid Cancer*: *Surgical Therapy* in this Discussion).[412] Postoperative EBRT or IMRT can be considered for: 1) unresectable primary Hürthle cell lesions that do not concentrate ^{131}I if disease is threatening vital structures; 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 follicular thyroid carcinoma.[3]

Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). The NCCN Guidelines provide algorithms 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 (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle cell [Thyroid] Carcinoma).

RAI therapy has been reported to decrease the risk of locoregional recurrence and is recommended for unresectable disease with positive ^{131}I imaging. Iodine 131 therapy (100–150 mCi) may be considered 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).[177] Pretreatment diagnostic imaging (^{123}I or low-dose ^{131}I) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) may be considered based on pathology, postoperative Tg, and intraoperative findings (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). However, some NCCN Panel Members did not feel that diagnostic total body imaging should be recommended before ^{131}I therapy is administered, because the thyroid remnant may interfere with the scan, making this a category 2B recommendation.[3]

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Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid.[413-416] 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 (MEN2A), which is the most common type; and 2) MEN2B.[417,418] Familial MTC is now viewed as a variant of MEN2A.[413,414,419] Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of the disease tend to present at earlier ages.[413,414] The 5-year relative survival for stages I to III is about 93%, whereas 5-year survival for stage IV is about 28%.[181,202] 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.[420] 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.[421] 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.[422-424] 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: 1) the expense of screening all thyroid nodules and only finding a few cases of MTC; 2) the lack of confirmatory pentagastrin stimulation testing; and 3) the resulting need for thyroidectomy in some patients who actually have benign thyroid disease.[425,426] 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.[415,416] 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[427] and because pentagastrin is no longer available in the United States. When MEN2A 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 MEN2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.

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All familial forms of MTC and MEN2 are inherited in an autosomal-dominant fashion. Mutations in the *RET* proto-oncogene are found in at least 95% of kindreds with MEN2A and 88% of familial MTC.[415,416,428] The *RET* proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; MEN2B and some familial MTC mutations are found within the intracellular exons 14 to 16.[413,414] 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 are 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.[429,430] Genetic testing for *RET* proto-oncogene mutations is recommended for all patients with newly diagnosed clinically apparent sporadic MTC, and for screening children and adults in known kindreds with inherited forms of MTC;[431] 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.[432]

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum carcinoembryonic antigen [CEA]) and screening of patients with germline *RET* proto-oncogene mutations for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A). 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, available at www.NCCN.org). Pheochromocytoma can be removed using laparoscopic adrenalectomy.[413,414,433] Preoperative thyroid and neck ultrasound (including central and lateral neck compartments) is recommended. Contrast-enhanced CT of chest and liver MRI or 3-phase CT of liver can be considered, although distant metastasis does not contraindicate surgery.[413,414] Liver imaging is rarely needed if the calcitonin is less than 400 pg/mL. Evaluation of vocal cord mobility can also be considered for patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.

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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 in the NCCN Guidelines for Thyroid Carcinoma).[9] The 8th edition of the AJCC Cancer Staging Manual separated MTC into its own stand-alone chapter.[9] Many of the studies cited in this Discussion reporting on AJCC-TNM staging have referred to the 5th edition of the AJCC-TNM staging[200] and not to the 6th, 7th, or 8th editions.[9,201,202]

However, the TNM staging classification lacks other important prognostic factors.[434] 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.[420,434] Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically

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are diagnosed at an earlier age) is probably similar to those with sporadic disease.[435,436] Despite an even younger typical age at diagnosis, however, patients with MEN2B who have MTC are more likely than those with MEN2A (or familial MTC) to have locally aggressive disease.[436]

Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor;[437] 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level;[438] and 3) postoperative residual hypercalcitoninemia.[439] 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.[434,440] Codon analysis is useful for predicting prognosis.[413,414,441] Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN2B, is associated with more aggressive disease.[442] More than 95% of patients with MEN2B have a mutation in exon 16 (codon 918), whereas 2% to 3% have a mutation in exon 15 (codon 883).[443]

Surgical Management

Surgery is the main treatment for MTC. While no curative systemic therapy for MTC is available, vandetanib and cabozantinib are recommended for locally advanced and metastatic MTC (see *Recurrent or Persistent Disease* in this Discussion).[444-447] MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, ^{131}I 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.[413,414]

Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease, because the possibility of MEN2 should dictate testing for a germline *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 (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org). 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).[376,420] 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.[413,414,448] Note that C634 mutations are the most common mutations.[413,414] Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN2B who have codon 883 *RET* mutations, 918 *RET* mutations, or compound heterozygous (V804M +

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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).[413,414,449]

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.[413,414,449,450] 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).[413,414,451,452] Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.[413,414,450,451,453] 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 MEN2A; longer follow-up is necessary to determine if these patients are cured.[454]

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.[413,414] A bilateral central neck dissection (level VI) can be considered for all patients with MEN2B. For those patients with MEN2A 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 MEN2B) 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 MEN2A 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 and IMRT have not been adequately studied as adjuvant therapy in MTC.[307,413,455] 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.[456] However, most centers do not have extensive experience with adjuvant EBRT or IMRT for this disease. While therapeutic EBRT or IMRT may be considered for grossly incomplete resection when additional attempts at surgical resection have been ruled out, adjuvant EBRT or IMRT is rarely recommended (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[413,414] EBRT or IMRT can also be given to palliate painful or progressing bone metastases.[309,310,394,413,414]

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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 MEN2A, and 6 patients with MEN2B), the 5- and 10-year survival rates were 90% and 86%, respectively.[457] 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.[439,458] 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.[459] 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.[460,461] 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.[461]

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 ultrasound is recommended. Patients with undetectable calcitonin levels and normal CEA 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 MEN2, annual screening for pheochromocytoma (MEN2B or MEN2A) and hyperparathyroidism (MEN2A) 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 (±PET) or MRI of the neck, chest, and abdomen with a liver protocol. Bone scan and MRI of axial skeleton should be considered in select patients such as those with very elevated calcitonin levels.[413,414] The NCCN Panel recognizes that many different

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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.[413,414]

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 active surveillance 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

Kinase inhibitors may be appropriate for select patients with recurrent or persistent MTC that is not resectable (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [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.[329,462,463] Vandetanib and cabozantinib are oral receptor kinase inhibitors that increase PFS in patients with metastatic MTC.[444,447,464-466]

Vandetanib is a multitargeted kinase inhibitor; it inhibits RET, vascular endothelial growth factor receptor (VEGFR), and endothelial growth factor receptor (EGFR).[444] In a phase III randomized trial in patients with unresectable, locally advanced, or metastatic MTC (n = 331), vandetanib increased PFS when compared with placebo (HR, 0.46; 95% CI, 0.31–0.69; $P < .001$); overall survival data are not yet available.[444] 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.[445] However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity.[467] 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).

Cabozantinib is a multitargeted kinase inhibitor that inhibits RET, VEGFR2, and MET. In a phase 3 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; $P < .001$).[447] Following long-term follow-up, the median overall survival for patients treated with cabozantinib was 26.6 months compared to 21.1 months for placebo, although this difference was not statistically significant (stratified HR, 0.85; 95% CI, .64–1.12, $P = .24$).[468] Exploratory analyses have suggested that cabozantinib may have a greater clinical benefit for medullary thyroid cancers harboring *RET* M918T or *RAS* mutations, although prospective trials are needed to confirm.[468,469] In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC.[446] 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 or IMRT. For unresectable locoregional disease that is symptomatic or progressing by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[470] the following options can be considered: 1) EBRT or IMRT; 2) vandetanib (category 1); or 3) cabozantinib (category

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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 active surveillance is acceptable given the lack of data regarding alteration in outcome. The NCCN Panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone.

In the setting of symptomatic disease or progression, the NCCN Panel recommends the following: 1) vandetanib (category 1);[444,466,471] 2) cabozantinib (category 1);[447] 3) clinical trial; or 4) consider other small-molecule kinase inhibitors (ie, sorafenib, sunitinib, lenvatinib, pazopanib) if clinical trials, vandetanib, or cabozantinib are not available or appropriate.[341,472-476] If the patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.[413,477-479] EBRT or IMRT can be used for local symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.[395-397] Best supportive care is also recommended.

Results from clinical trials have shown the effectiveness of novel multitargeted therapies including sunitinib,[341,342] sorafenib,[402,473] lenvatinib,[476] and pazopanib[475] in MTC. Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.[364,367,399,403] Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.[364]

Novel therapies and the management of aggressive MTC have been reviewed.[323,413,480-483] 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.[471] A phase 2 trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with ^{131}I.[484] Overall survival was improved in the subset of patients with increased calcitonin doubling times.[485]

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas (ATCs) are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[486] Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[487] Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[129,487] The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.[486,488] As previously mentioned, anaplastic carcinoma is the least common type of thyroid carcinoma. An average of 63,229 patients/year were diagnosed with thyroid carcinoma between 2010 to 2014. Of these 63,229 patients, only 514 patients (0.8%) had anaplastic carcinoma.[29]

Approximately 50% of patients with ATC 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.[489] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Iodine deficiency is associated with ATC. More than 80% of patients with ATC have a history of goiter.[488,490,491] Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not.

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Therefore, ^{131}I imaging cannot be used and RAI treatment is not effective in these patients with ATC.[488]

ATC is typically diagnosed based on clinical symptoms, unlike differentiated thyroid carcinoma, which is typically diagnosed after FNA on a suspicious thyroid nodule. Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner's syndrome, stroke, and hoarseness due to vocal cord paralysis.[492] Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[407,493] 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.

Diagnosis

The diagnosis of ATC is usually established by core or surgical biopsy. If FNA is suspicious or not definitive, core or surgical biopsy should be performed to establish the diagnosis of ATC.[488] The appearance of ATCs varies widely; many ATCs have mixed morphologies. The most common morphology is biphasic spindle and giant cell tumor. Molecular techniques are not recommended for diagnosis of ATC.[488] Sometimes it is difficult to discriminate between ATC and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[114,488]

Diagnostic procedures include a complete blood count (CBC) with differential, comprehensive chemistry, TSH level, direct exam of larynx with evaluation of vocal cord mobility, and imaging studies. Neck ultrasound can rapidly assess tumor extension and invasion.[492] CT scans of the head, neck, chest, abdomen, and pelvis can accurately determine the extent of the thyroid tumor and identify tumor invasion of the great vessels and upper aerodigestive tract structures.[494] PET/CT scans from skull base to mid-thigh are recommended to accurately stage the patient. Bone metastases are usually lytic. All ATCs are considered stage IV (A, B, or C) (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma).[9] Clinically apparent anaplastic tumors are usually unresectable.

Prognosis

No curative therapy exists for ATC; it is almost uniformly fatal.[495,496] The median survival from diagnosis is about 5 months.[488,497] The 1-year survival rate is about 20%.[493,497] 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.[498] 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.[499] Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, white blood cell (WBC) count ≥10,000 mm^3, and dyspnea as a presenting symptom.[500,501]

Treatment

ATC has a very poor prognosis and responds poorly to conventional therapy. The role of palliative and supportive care is paramount and should be initiated early in the disease. At the outset of the diagnosis, it is critical that conversations about end-of-life care be initiated so that a clear understanding of how to manage the airway is undertaken, which is clear to the family and all providers. Tracheostomy is often a morbid and temporary treatment of the airway and may not be the option a patient would choose.[498,502]

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Surgery

Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.[486] Before resection is attempted, the extent of disease—particularly in the larynx, trachea, and neck—should be accurately assessed by a very experienced surgeon who is capable of performing extensive neck dissections if necessary. However, most patients with ATC have unresectable or metastatic disease. The patency of the airway should be assessed throughout the patient's course.[498] 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.[497,499,503,504] Patients need to receive levothyroxine if total thyroidectomy is done.

Radiation Therapy

EBRT or IMRT can increase short-term survival in some patients; EBRT or IMRT can also improve local control and can be used for palliation (eg, to prevent asphyxiation).[455,486,488,501,505-509] Surgical excision or external irradiation should be considered for isolated skeletal metastases. For solitary brain lesions, either neurosurgical resection or radiation therapy is recommended. Once brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months. Enteral nutrition may be useful for some patients who have difficulty swallowing (see *Principles of Nutrition: Management and Supportive Care* in the NCCN Guidelines for Head and Neck Cancer, available at www.NCCN.org). If enteral feeding is considered, a careful conversation should occur with the patient about their wishes.

Systemic Therapy

Treatment with single-drug chemotherapy is not very effective, although some patients may show disease response or have stable disease.[488,509] Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year.[510] Distant metastases then become the leading cause of death.[511] 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.[509,512-514] IMRT may be useful to reduce toxicity.[455,488,515-519] 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).[488,520] Recommended regimens include paclitaxel and carboplatin combinations, docetaxel and doxorubicin combinations, paclitaxel alone, or doxorubicin alone.[488,521] Dabrafenib plus trametinib combination or larotrectinib are also options for *BRAF* V600E mutation-positive or *NTRK* gene fusion-positive tumors, respectively.[355,522] The NCCN Panel recommends molecular testing to help inform decisions regarding systemic therapy and to determine eligibility for clinical trials. The dosage and frequency of administration of all the recommended systemic therapy agents are provided in the algorithm. 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.[488]

Systemic therapy alone can be considered for patients with unresectable or metastatic disease. Single-agent doxorubicin is the only agent that is

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approved by the FDA for ATC.[488] Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease.[523-525] 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.[488,525]

A phase 2, open-label trial of 16 patients with *BRAF* V600E-mutated ATC evaluated the efficacy and safety of dabrafenib 150 mg, twice daily, in combination with trametinib 2 mg, once daily.[522] The confirmed overall response rate (ORR) was 69% (95% CI, 41%–89%), with 7 responses ongoing. While duration of response, PFS, and OS were not yet reached, the 12-month estimates were 90%, 79%, and 80%, respectively. The combination was found to be well-tolerated as evaluated in 100 patients across 7 rare tumor types; common adverse events included fatigue (38%), pyrexia (37%) and nausea (35%).[522] Based on these data, the FDA approved dabrafenib/trametinib for ATC with *BRAF* V600E mutation on May 4, 2018.[526]

A pooled analysis of 3 studies (a phase 1 including adults, a phase 1/2 involving children, and a phase 2 involving adolescents and adults) studied the safety and efficacy of larotrectinib in patients with *NTRK* gene fusion-positive tumors, including 7 patients with thyroid cancer of which 1 patient had ATC.[355,527] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment.[355,527] 100% of the thyroid cancers in this study responded to larotrectinib, with 1 complete response and 4 partial responses.[527] Larotrectinib was found to be well-tolerated as the majority (93%) of adverse events were grades 1 or 2 and no treatment-related adverse events of grades 3 or 4 occurred in more than 5% of patients.[355] Based on these data, the FDA approved larotrectinib for metastatic solid tumors with *NTRK* gene fusion and no satisfactory alternative treatments on November 26, 2018.[528]

Given the poor outcome with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials. Previous clinical trials for ATC have tested therapies including fosbretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin [EPC2407], which are vascular disrupting agents), efatutazone (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.[342,520,529-536] A 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).[520,537]

Multimodality therapy is recommended in patients with locally resectable disease (see *Primary Treatment* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[488,515,520,538-542] Retrospective studies have reported that patients with ATC who receive trimodal therapy including surgery, radiation, and systemic therapy demonstrate improved survival compared to those who undergo less aggressive treatment approaches.[543,544] 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.[545] Preliminary data suggest that ALK inhibitors may be effective in a subset of patients with papillary thyroid cancer who have ALK gene fusions; however, these ALK gene fusions are rarely reported in patients with ATC.[356-359] *BRAF* mutations have been reported in patients with ATC,[492,546-548] supporting the utility of the BRAF V600E inhibitor, dabrafenib in combination with the MEK inhibitor, and trametinib for treatment of this disease.[522]

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