National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thyroid Carcinoma

Version 1.2025 — March 27, 2025

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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.

Updates in Version 1.2025 of the NCCN Guidelines for Thyroid Carcinoma from Version 5.2024 include:

THYR-1
- Middle pathway, column 2 added: High clinical and/or radiographic suspicion of malignancy
- Middle pathway, no, primary treatment, bullet 3 modified: Consider nodule surveillance if low risk or patient preference ~~as recommended by the ATA or TI-RADS~~
- Lower pathway, no, primary treatment, bullet 4 modified: Consider nodule surveillance ~~as recommended by the ATA or TI-RADS~~
- Footnote b modified:... (approximately ~~5~~*4*% 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 *for molecular testing if available*.
- Footnote f modified: Total thyroidectomy may be considered for ~~oncocytic neoplasm (Bethesda IV),~~ history of radiation exposure or contralateral lobe lesions.

THYR-2
- Footnote j modified: Clinical risk factors, sonographic patterns, *reported risk of malignancy based on molecular test*, and patient preference can help determine whether nodule surveillance or surgery is appropriate. *See Principles of Active Surveillance for Low-risk Papillary Thyroid Cancer.*

PAP-1
- Page extensively modified

PAP-2
- Column 2, bullet 1 modified: Thyroid and neck ultrasound (including central and lateral *cervical nodal* compartments), if not previously done
- Column 2, bullet 2 modified: Biopsy suspicious lymph nodes or contralateral lesions *that meet sonographic criteria by ATA and TI-RADS*
- Column 3, upper pathway, bullet removed: Tumor >4 cms
- Column 3, middle pathway, bullet 1 added: Tumor >4 cm
- Column 3, lower pathway, bullet removed: Tumor ≤4 cm in diameter
- Footnote m modified: ~~1 cm or less, without other high-risk features.~~ *The diagnosis of follicular carcinoma or oncocytic 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) 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. Given the challenges of cytology to explicitly diagnose medullary thyroid carcinoma (MTC) in limited samples, molecular tests may be used to identify them. 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 4% 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 for molecular testing if available.*
- Footnote n added: 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).

PAP-3
- Unresectable pathway modified
  - For ~~viscerally~~ *locoregional* invasive disease or rapid progression, ~~upfront~~ *consider* external beam radiation therapy (EBRT), or ~~neoadjuvant~~ *systemic* therapy ~~may be most appropriate~~
  - Iodine-123 or iodine-131 total body radioiodine imaging ~~with TSH stimulation (thyroid hormone withdrawal or recombinant human TSH [rhTSH])~~
  - ~~Post-treatment iodine-131 whole body imaging~~

PAP-4
- RAI not typically recommended (if all present), bullet 6 modified: Postoperative unstimulated Tg <1 ng/mL ~~or stimulated Tg <2 ng/mL~~
- RAI selectively recommended (if any present)

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Thyroid Carcinoma from Version 5.2024 include:

- Bullet 1 modified: ~~Primary tumor >2 cm~~ *Large primary tumor size*
- Bullet 4 modified: Cervical lymph node metastases *(millimetric central nodes)*

• Column 2, paragraph 1 modified: RAI ~~is~~ *may* not *be* required in patients with classic...
• Gross residual ~~not amenable to RAI therapy~~ *RAI-refractory disease*
• Footnotes modified
- v: eg, tall cell, columnar cell, hobnail ~~variants~~, diffuse sclerosing, ~~insular~~ *solid/trabecular.*
- w: Minimal extrathyroidal extension alone likely does not warrant RAI. *This is seen by the surgeon during thyroid resection.*
- y: Differentiated high-grade carcinoma includes PTCs with ≥5 mitoses per 2 mm^2 and/or tumor necrosis. *There is a lack of data regarding benefit of RAI in isolation with these features.*

• Footnote added: There are no data for a specific size cut-off; >4 cm may be considered, although data are conflicting.

PAP-5
• Upper pathway, column 4: Consider pretreatment neck imaging *if postoperative Tg is higher than expected*
• Upper pathway, column 6, bullet removed: Post-treatment iodine-131 imaging (whole body RAI scan)
• Footnote removed: If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

PAP-6
• Column 4: At least 4–6 weeks following ~~CT with contrast~~ *imaging*
• Column 5, lower pathway: No uptake *or not performed*
• Column 6, upper pathway, bullet 1: RAI therapy ~~and post-treatment imaging (whole body RAI scan)~~
• Column 6, lower pathway, bullet 1: Consider RAI adjuvant therapy ~~and post-treatment imaging (whole body RAI scan, consider PET scan)~~
• Footnote removed:Thyrotropin alfa may be used for elderly patients for when prolonged hypothyroidism may be risky.

PAP-8
• Page extensively modified

PAP-9
• Progressively rising Tg (basal or stimulated), pathway removed (also for FOLL-8)
• Middle pathway, column 3: Consider ~~radioiodine~~ *RAI* ~~treatment~~ *therapy*, if ~~postoperative radioiodine imaging positive~~ *preoperative or postoperative radioiodine imaging positive* (Also for FOLL-8)

PAP-10/11/12
• Page extensively modified

FOLL-1
• Column 2, bullet 1: Thyroid and neck ultrasound (including central and lateral *cervical nodal* compartments), if not previously done (also for MEDU-2 and MEDU-3)
• Column 2, bullet 2: *Consider* CT/MRI...

FOLL-2
• Unresectable, lower pathway: For ~~viscerally~~ *locoregional* invasive disease or rapid progression, ~~upfront~~ *consider* EBRT, ~~neoadjuvant~~ *or systemic* therapy ~~may be most appropriate~~
• Unresectable, upper and lower pathway, bullet 2: Iodine-123 or iodine-131 total body radioiodine imaging ~~with TSH stimulation (thyroid hormone withdrawal or rhTSH)~~
• Unresectable, RAI uptake present, upper and lower pathway, bullet removed: Post-treatment iodine-131 whole body imaging

FOLL-3
• RAI not typically recommended (if all present), bullet 6: Postoperative unstimulated Tg <1 ng/mL ~~or stimulated Tg <2 ng/mL~~
• RAI selectively recommended (if any present)

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Thyroid Carcinoma from Version 5.2024 include:

- Bullet removed: Primary tumor >2 cm
- Bullet 1 added: Large primary tumor size
- Bullet 3 modified: Cervical lymph node metastases *(millimetric central nodes)*

• Footnotes
- q: Minimal extrathyroidal extension alone likely does not warrant RAI. *This is seen by the surgeon during thyroid resection.*
- s: Differentiated high-grade carcinoma includes follicular thyroid carcinoma with ≥5 mitoses per 2 mm^2 and/or tumor necrosis. *There is a lack of data regarding benefit of RAI in isolation with these features.*
- Footnote u added: There are no data for a specific size cut-off; >4 cm may be considered, although data are conflicting.

FOLL-4
• Upper pathway, column 6, bullet removed: Post-treatment iodine-131 imaging (whole body RAI scan)

FOLL-5
• Column 4: At least 4–6 weeks following ~~CT with contrast~~ *imaging*
• Column 5, lower pathway: No uptake *or not performed*
• Column 6, upper pathway, bullet 1: RAI therapy ~~and post-treatment imaging (whole body RAI scan)~~
• Column 6, lower pathway, bullet 1: Consider RAI adjuvant therapy ~~and post-treatment imaging (whole body RAI scan, consider PET scan)~~
• Footnote removed: Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

FOLL-7/9/10/11
• Page extensively modified

ONC
• Section extensively modified

MEDU-1
• Clinical presentation, lower pathway: Germline mutation of RET *pathologic variant (PV)*
• Diagnostic procedures, upper pathway
- Bullet 5: Screen for germline RET PV (exons *8*, 10, 11, 13–16)
- Bullet 6: Thyroid and neck ultrasound (including central and lateral *cervical nodal*)
- Sub-bullet 1: Consider *if calcitonin is >300 pg/mL*, contrast-enhanced CT of neck/chest and liver MRI or 3-phase CT of liver

• Column removed: <1.0 cm in diameter and unilateral thyroid disease
• Column removed: ≥1.0 cm in diameter or bilateral thyroid disease
• Primary treatment
- Bullet 1: Total thyroidectomy with ~~bilateral~~ central neck dissection (level VI)
- Bullet 4 added: Lobectomy can be considered in select case without germline *RET* mutation if no concerns for abnormal adenopathy and contralateral nodules

• Footnote added: High-grade pathologic features include tumor necrosis and an elevated mitotic count or Ki67 proliferation index.

MEDU-2
• Additional workup, bullet 4 modified: Central and lateral ~~neck~~ *cervical nodal* compartments ultrasound, if not previously done

MEDU-3
• Primary treatment
- Bullet 1: Total thyroidectomy during ~~the first year of life~~ *childhood* or at diagnosis
- Bullet 2 added: Surgery recommended during the first year of life for patients with codon M918T mutations
- Bullet 3 added: Surgery recommended before age 5 for patients with codon A883F mutations.

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Thyroid Carcinoma from Version 5.2024 include:

- Bullet 4: Therapeutic neck dissection ~~as indicated; consider prophylactic bilateral central neck dissection (level VI)~~ *guided by imaging*
- Bullet 5 added: Consider prophylactic central neck dissection (level VI)

• Additional workup, upper pathway, bullet 4 modified: Central and lateral ~~neck~~ *cervical nodal* compartments ultrasound, if not previously done

• Footnote j: ...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 *most* other RET PVs associated with MEN2A or FMTC are generally moderate risk. *Codon V804M mutations are common but carry a low lifetime risk of MTC (~4%)....*

MEDU-4

• Page extensively modified

MEDU-5

• Upper pathway, column 3, bullet 3: Consider ~~bone scan and~~ whole body MRI in patients with very elevated calcitonin levels

• Footnote added: The ATA Guidelines recommend T/L spine and pelvis MRI. Wells SA, et al. Thyroid 2015;25:567-610.

MEDU-6/7

• Pages extensively modified

ANAP-2

• Footnotes removed
  - Adjuvant/Radiosensitizing Chemotherapy Regimens for Anaplastic Thyroid Carcinoma (ANAP-A [1 of 4]).
  - Regimens that may be used for neoadjuvant therapy include dabrafenib/trametinib for BRAF V600E mutations; selpercatinib or pralsetinib for RET gene fusion-positive tumors; and larotrectinib or entrectinib for patients with NTRK gene fusion-positive tumors.

ANAP-3

• Footnotes
  - Removed: 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. Oral presentation at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27-October 1, 2019.); or pembrolizumab for TMB-H (Marabelle A, et al. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019).
  - Removed: Systemic Therapy Regimens for Metastatic Disease (ANAP-A [2 of 4]).
  - g: 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. ~~An FDA-approved biosimilar is an appropriate substitute for denosumab.~~ *An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.*

ANAP-A

• Section removed from Guidelines

THYR-B 1 of 5

• Systemic therapy tables added, section extensively modified.

THYR-C 1 of 5

• Bullet 2: 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.~~ *Preparation with either thyroid hormone withdrawal or with thyrotropin alfa may be used for*

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Thyroid Carcinoma from Version 5.2024 include:

treatment of patients with distant metastases. While thyrotropin alfa is not FDA approved for treatment of distant metastases, a recent meta-analysis reported there was no significant impact on the effectiveness of I-131 therapy for metastatic thyroid cancer depending between either preparation.

- Bullet 3: ... ~~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~~. *If performed, 24-hour urine collection may document adequate iodine restriction (urine iodine <50 mcG). The diet involves a* ~~10~~7-to 14-day reduction in intake of iodized salt, seafood, and dairy products with the intention of optimizing the sensitivity of diagnostic examinations and the efficacy of potential therapies that may follow. Excellent resource information can be found at ThyCa.org and LIDLifeCommunity.org.
- Bullet 10: Other organizations have defined RAI-refractory disease as: *in the presence of structural disease*...

THYR-C 2 of 5
- Administered activity, sub-bullet 1: 30–*50* mCi
- Special circumstances
  - sub-bullet 1: Wait 2 months to allow for free iodine levels to decrease ~~(<100 mcg/24 hours)~~ and allow for optimal RAI uptake.
  - sub-bullet 3: Wait ~~3~~2–6 months after cessation of lactation or with normalization of serum prolactin levels.
  - sub-bullet 4: Complete cessation of breastfeeding after ~~iodine-123 or~~ iodine-131 administration...

THYR-C 5 of 5
- References removed
  - Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, et al. Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. Thyroid 2012;22:310-317.
  - Tala H, Robbins R, Fagin JA, et al. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. J Clin Endocrinol Metab 2011;96:2105-2111.
- References added
  - Giovanella L, Garo ML, Campenni A, et al. Thyroid hormone withdrawal versus recombinant human tsh as preparation for i-131 therapy in patients with metastatic thyroid cancer: A systematic review and meta-analysis. Cancers (Basel) 2023;15:2510.
  - Kim HK, Lee SY, Lee JI, et al. Usefulness of iodine/creatinine ratio from spot-urine samples to evaluate the effectiveness of low-iodine diet preparation for radioiodine therapy. Clin Endocrinol (Oxf) 2010;73:114-118.
  - Robbins RJ, Schlumberger MJ. The evolving role of (131)i for the treatment of differentiated thyroid carcinoma. J Nucl Med 2005;46 Suppl 1:28S-37S.
  - Li JH, He ZH, Bansal V, Hennessey JV. Low iodine diet in differentiated thyroid cancer: A review. Clin Endocrinol (Oxf) 2016;84:3-12.

THYR-D
- Active Surveillance should not be used in the following scenarios, bullet 2: Tumor characteristics: Aggressive histologic subtypes (if noted on FNA); invasion of recurrent laryngeal nerve, trachea, or esophagus; visible extrathyroidal extension; regional or distant metastases; tumor near posterior capsule; *tumors invading the isthmus or abutting against the trachea.*

THYR-E
- Paragraph 1: *Papillary and* follicular thyroid cancer...
- Paragraph 2 added: Familial Adenomatous Polyposis...
- Section added: Hereditary thyroid cancer syndromes...

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Ali SZ, Baloch ZW, Cochand-Priollet B, et al. Thyroid 2023;33:1039-1044. https://pubmed.ncbi.nlm.nih.gov/37427847/. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

FNA RESULTS → TREATMENT[e]

Malignant or suspicious for malignancy (Bethesda V or VI)[i]
- Papillary or suspicious for papillary → Primary Treatment (PAP-1)
- Medullary or suspicious for medullary → Primary Treatment (MEDU-1)
- Anaplastic or suspicious for anaplastic → Primary Treatment (ANAP-1)

Follicular or Oncocytic neoplasm[a,b] (Bethesda IV)[d] → High clinical and/or radiographic suspicion of malignancy[d]
- Yes → Consider lobectomy or total thyroidectomy[f] for definitive diagnosis/treatment → PAP-1, FOLL-1, ONC-1
- No →
  - Consider diagnostic lobectomy → PAP-1, FOLL-1, ONC-1
  - Consider molecular diagnostics[b] (THYR-2)
  - Consider nodule surveillance if low risk or patient preference[g]

Atypia of undetermined significance[b,c] (AUS) (Bethesda III) → High clinical and/or radiographic suspicion of malignancy[d]
- Yes → Consider lobectomy or total thyroidectomy[f] for definitive diagnosis/treatment → PAP-1, FOLL-1, ONC-1
- No →
  - Consider repeat fine-needle aspiration (FNA)[h]
  - Consider molecular diagnostics[b] (THYR-2)
  - Consider diagnostic lobectomy (if Bethesda III on 2 or more occasions)
  - Consider nodule surveillance[g]

  → PAP-1, FOLL-1, ONC-1

[a] Bethesda v3 terminology for Bethesda IV is follicular neoplasm or oncocytic follicular neoplasm, and the estimated risk of malignancy, inclusive of noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP), is mean 30% (range, 23%–34%).

[b] The diagnosis of follicular carcinoma or oncocytic 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) 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. Given the challenges of cytology to explicitly diagnose medullary thyroid carcinoma (MTC) in limited samples, molecular tests may be used to identify them. 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 4% 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 for molecular testing if available.

[c] Estimated risk of malignancy is mean 22% (range, 13%–30%) inclusive of NIFTP.

[d] Based on rapid growth of nodule, imaging, physical examination, 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 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.

[i] Bethesda V Estimated risk of malignancy, inclusive of NIFTP, mean 74% (range, 67%–83%); Bethesda VI estimated risk of malignancy, inclusive of NIFTP, mean 97% (range, 97%–100%); Ali SZ, et al. Thyroid 2023;33:1039-1044.

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

MOLECULAR DIAGNOSTIC RESULTS[a]

TREATMENT[g]

AUS[a] (Bethesda III)[c] or Follicular neoplasm (Bethesda IV)[a,b]

- **Molecular diagnostics indicate benign lesion[b]** → **Nodule surveillance[g,j]**
- **Molecular diagnostics not informative or with insufficient or degraded sample** → **Nodule surveillance[g,j] or Consider lobectomy in select situations for definitive diagnosis/treatment or Consider repeat biopsy**
- **Molecular diagnostics suggestive of malignancy** → **Consider lobectomy or total thyroidectomy (depending on molecular results)[b] for definitive diagnosis/treatment or Nodule surveillance[g,j]**

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Ali SZ, Baloch ZW, Cochand-Priollet B, et al. Thyroid 2023;33:1039-1044. https://pubmed.ncbi.nlm.nih.gov/37427847/. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

[a] Bethesda v3 terminology for Bethesda IV is follicular neoplasm or oncocytic follicular neoplasm, and the estimated risk of malignancy, inclusive of NIFTP, is mean 30% (range, 23%–34%).

[b] The diagnosis of follicular carcinoma or oncocytic 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) 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. Given the challenges of cytology to explicitly diagnose MTC in limited samples, molecular tests may be used to identify them. 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 4% 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 for molecular testing if available.

[c] Estimated risk of malignancy is mean 22% (range, 13%–30%) inclusive of 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).

[j] Clinical risk factors, sonographic patterns, reported risk of malignancy based on molecular test, and patient preference can help determine whether nodule surveillance or surgery is appropriate. See Principles of Active Surveillance for Low-risk Papillary Thyroid Cancer (THYR-D).

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

FNA RESULTS	DIAGNOSTIC PROCEDURES	PREOPERATIVE OR INTRAOPERATIVE DECISION-MAKING CRITERIA	PRIMARY TREATMENT	
Papillary carcinoma or suspicious for papillary carcinoma →	• Thyroid and neck ultrasound (including central and lateral cervical nodal compartments), if not previously done • Consider CT/MRI with contrast when suspicious nodes in the neck are detected by ultrasound[f] and/or vocal cord paresis[a] • Consider assessment of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)[b] • FNA for suspicious lateral neck nodes[c] • Screen for personal and/or family history suggestive of inherited cancer risk[g] →	Indications for total thyroidectomy (any present): • Known distant metastases • Extrathyroidal extension • Lateral cervical lymph node metastases or gross central neck lymph node metastases • Poorly differentiated and differentiated high-grade carcinoma • Consider for prior radiation exposure (category 2B) • Consider for bilateral nodularity or tumors >4 cm in diameter →	• Total thyroidectomy • Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease[d] →	Postsurgical Evaluation (PAP-3)
		Indications for total thyroidectomy or lobectomy, if all criteria present: • No prior radiation exposure • No distant metastases • No lateral cervical lymph node metastases • No extrathyroidal extension • Tumor 1–4 cm in diameter →	Total thyroidectomy (category 2B) →	Postsurgical Evaluation (PAP-3)
			Lobectomy[e] (preferred) + isthmusectomy (category 2B) →	Post- Lobectomy (PAP-2)

[a] Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in radioactive iodine (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.
[f] Principles of Active Surveillance for Low-Risk Papillary Thyroid Cancer (THYR-D).
[g] Principles of Cancer Risk Assessment and Counseling (THYR-E).

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

CLINICAL PRESENTATION[l]

PRIMARY TREATMENT

Post-lobectomy[m] →

- **Thyroid and neck ultrasound (including central and lateral cervical nodal compartments), if not previously done**
- **Biopsy suspicious lymph nodes or contralateral lesions that meet sonographic criteria by ATA and TI-RADS[n]**

→ **Any of the following:**
- **Gross positive resection margins**
- **Gross extra-thyroidal extension**
- **Confirmed nodal metastasis[h]**
- **Confirmed contralateral disease**
- **Vascular invasion**

→ **Completion of thyroidectomy**
- **Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease if not previously done**

→ **Postsurgical Evaluation (PAP-3)**

→ **Any of the following:**
- **Tumor >4 cm**
- **Lymphatic invasion**
- **Macroscopic multifocal disease (>1 cm)**
- **Poorly differentiated and differentiated high-grade carcinoma**

→ **Completion of thyroidectomy** → **Postsurgical Evaluation (PAP-3)**

or

Disease monitoring[j] (category 2B) → **Consider levothyroxine therapy to keep thyroid stimulating hormone (TSH) low or normal[k]**

→ **All of the following:**
- **Negative resection margins**
- **No contralateral lesion**
- **No suspicious lymph node**

or
- **NIFTP[i]**

→ **Disease monitoring[j]** → **Consider levothyroxine therapy to keep TSH normal[k]** → **Disease Monitoring and Maintenance (PAP-7)**

[h] Completion of thyroidectomy is not required for incidental small volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm) (see PAP-4).
[i] Formerly called encapsulated follicular variant of PTC, NIFTP has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.
[j] Measurement of Tg and Tg ab may be useful for obtaining a postoperative baseline; however, data to interpret Tg and Tg ab in the setting of an intact thyroid lobe are lacking.
[k] Principles of TSH Suppression (THYR-A).
[l] The diagnosis of follicular carcinoma or oncocytic 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) 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. Given the challenges of cytology to explicitly diagnose MTC in limited samples, molecular tests may be used to identify them. 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 4% 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 for molecular testing if available.
[m] If histology demonstrates cribriform-morular variant, screen for FAP. See Principles of Cancer Risk Assessment and Counseling (THYR-E).
[n] 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).

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

POSTSURGICAL EVALUATION

No gross residual disease in neck → Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (PAP-4)

Gross residual disease in neck → Cross-sectional CT or MRI of neck with contrast

- **Resectable** → Resect, if possible
  - No gross residual disease → Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (PAP-4)
  - Gross residual disease →
    - TSH + Tg measurement + antithyroglobulin antibodies (Tg ab) (6–12 weeks postoperatively)
    - Iodine-123 or iodine-131[p] total body radioiodine imaging (category 2B)
      - RAI uptake absent[s] → Monitoring of residual disease or Consider EBRT if disease is threatening vital structures[q] or Consider RAI therapy[q]
      - RAI uptake present[r] or No RAI imaging performed →
        - RAI therapy (preferred)[q]
        - TSH-stimulated Tg
        - Consider EBRT[q]
- **Unresectable[o]** →
  - TSH + Tg measurement + antithyroglobulin antibodies (Tg ab) (6–12 weeks postoperatively)
  - Iodine-123 or iodine-131[p] total body radioiodine imaging (category 2B)
    - (see above)
  - **Unresectable[o]** → For locoregional invasive disease or rapid progression, consider external beam radiation therapy (EBRT), systemic therapy[q] →
    - TSH + Tg measurement + Tg ab (6–12 weeks postoperatively)
    - Iodine-123 or iodine-131[p] total body radioiodine imaging (category 2B)
      - RAI uptake absent[s] → Monitoring of residual disease or Consider systemic therapy (PAP-10) or Consider RAI therapy[q]
      - RAI uptake present[r] or No RAI imaging performed →
        - RAI therapy (preferred)[q]
        - TSH-stimulated Tg

All of the above →
- Suppress TSH with levothyroxine[k]
- Disease Monitoring and Maintenance (PAP-7)

[k] Principles of TSH Suppression (THYR-A).
[o] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.
[p] If considering dosimetry, iodine-131 is the preferred agent.
[q] Principles of Radiation and RAI Therapy (THYR-C).
[r] If higher than expected uptake (residual thyroid uptake or distant metastasis), change dose accordingly.
[s] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.

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

CLINICOPATHOLOGIC FACTORS

CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

RAI not typically recommended (if all present):
- Papillary thyroid carcinoma (PTC), classic subtype
- Largest primary tumor ≤2 cm
- Intrathyroidal
- Unifocal or multifocal (all foci ≤1 cm)
- No detectable Tg ab
- Postoperative unstimulated Tg <1 ng/mL[t]
- Negative postoperative ultrasound, if done[u]

→ RAI not typically indicated (PAP-7)

RAI selectively recommended (if any present):
- Large primary tumor size[z]
- High-risk subtypes[v]
- Lymphatic invasion
- Cervical lymph node metastases (millimetric central nodes)
- Macroscopic multifocality (one focus >1 cm)
- Postoperative unstimulated Tg 1–10 ng/mL[t]
- Microscopic positive margins

→ RAI may not be 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 Tg ab → RAI not typically indicated (PAP-7)

→ RAI is recommended when the combination of individual clinical factors (such as the extent 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 Based on Clinicopathologic Features (PAP-5)

RAI typically recommended (if any present):
- Significant N1b disease
- Gross extrathyroidal extension[w]
- Postoperative unstimulated Tg >10 ng/mL[t,x]
- Bulky or >5 positive lymph nodes
- Vascular invasion
- Differentiated high-grade carcinoma[y]

→ RAI Being Considered Based on Clinicopathologic Features (PAP-5)

Known or suspected distant metastases at presentation → Amenable to RAI (PAP-6)

Gross residual RAI-refractory disease → (PAP-10)

[t] Tg values obtained 6–12 weeks after total thyroidectomy.
[u] If preoperative imaging incomplete, postoperative imaging should evaluate central and lateral neck.
[v] eg, tall cell, columnar cell, hobnail, diffuse sclerosing, solid/trabecular.
[w] Minimal extrathyroidal extension alone likely does not warrant RAI. This is seen by the surgeon during thyroid resection.
[x] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT [with contrast if there is concern about mediastinal lymph node metastases]) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.
[y] Differentiated high-grade carcinoma includes PTCs with ≥5 mitoses per 2 mm^2 and/or tumor necrosis. There is a lack of data regarding benefit of RAI in isolation with these features.
[z] There are no data for a specific size cut-off; >4 cm may be considered, although data are conflicting.

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

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

RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → Clinicopathologic findings prompting consideration for RAI, without gross residual disease or known distant metastasis (PAP-4)

- → RAI therapy indicated based on pathology → Consider pretreatment neck imaging if postoperative Tg is higher than expected[s] → Resect clinically significant structural disease if possible → • RAI therapy for remnant ablation or adjuvant therapy[q,aa] → • Disease Monitoring and Maintenance (PAP-7) • Levothyroxine to appropriate TSH target (THYR-A)
- → RAI therapy not indicated based on pathology → • Disease Monitoring and Maintenance (PAP-7) • Levothyroxine to appropriate TSH target (THYR-A)

[q] Principles of Radiation and RAI Therapy (THYR-C).
[s] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
[aa] 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). Patients on dialysis require special handling.

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

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

6–12 weeks post-thyroidectomy → **Known or suspected distant metastases at presentation or elevated Tg (PAP-4)** →
- **Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci[bb,dd]**
- **Resect clinically significant structural disease if possible**

→ **At least 4–6 weeks following imaging[cc]:**
- **Consider pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with TSH stimulation[q,aa]**

→ **Confirmed radioiodine-avid tumor or Thyroid remnant uptake only** →
- **RAI therapy[q] Consider other local therapies (EBRT,[q] etc) as primary therapy or postoperative for structural metastatic disease**

→ **No uptake or not performed** →
- **Consider RAI adjuvant therapy[q] Consider other local therapies (EBRT,[q] etc) as primary therapy or postoperative for structural metastatic disease**

→
- **Disease Monitoring and Maintenance (PAP-7)**
- **Levothyroxine to appropriate TSH target (THYR-A)**

[q] Principles of Radiation and RAI Therapy (THYR-C).
[aa] 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. Patients on dialysis require special handling.
[bb] To evaluate macroscopic metastatic foci for potential alterative therapies (eg, surgical resection, EBRT) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.
[cc] Consider 24-hour urine iodine.
[dd] If suspicion of pulmonary metastasis, chest CT can be done without contrast.

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

TREATMENT	DISEASE MONITORING	FINDINGS	MANAGEMENT	
Lobectomy	• Physical examination • TSH • Neck ultrasound at 6–12 months	Abnormal contralateral nodule or lymph node	Biopsy of suspicious areas (if lymph node, consider Tg washout)	Clinical Presentation (PAP-2)
		No evidence of disease	• Physical examination • Neck ultrasound as clinically indicated See NCCN Guidelines for Survivorship	Recurrent Disease (PAP-9) or Metastatic Disease (PAP-10)
Total thyroidectomy without RAI	• Physical examination • TSH • Tg measurement and Tg ab at 6–12 weeks • Neck ultrasound at 6–12 months	Rising or new Tg ab	Consider additional imaging (CT neck/chest), PET, or RAI imaging	Recurrent Disease (PAP-9)
		Abnormal imaging and/or rising Tg	Biopsy of suspicious areas on imaging (consider Tg washout)	Recurrent Disease (PAP-9)
		No evidence of disease	• Physical examination • TSH (goal based on risk stratification) • Tg measurement and Tg ab annually if stable • Neck ultrasound as clinically indicated See NCCN Guidelines for Survivorship	Recurrent Disease (PAP-9) or Metastatic Disease (PAP-10)

Total thyroidectomy with RAI (PAP-8)

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

TREATMENT	DISEASE MONITORING	FINDINGS	MANAGEMENT	
Total thyroidectomy with RAI →	• Physical examination • Neck ultrasound at 6–12 months • TSH • Tg measurement and Tg ab[ee]	Rising or new Tg ab[ff] →	Consider additional imaging (CT neck/chest), PET, or RAI imaging	→ Recurrent Disease (PAP-9)
		Abnormal imaging and/or rising Tg →	Consider biopsy of suspicious areas on imaging with Tg washout. Follow-up imaging of known iodine-avid disease with cross-sectional imaging (CT or MRI).	→ Recurrent Disease (PAP-9)
		No evidence of disease →	• Physical examination • TSH[k] • Tg measurement and Tg ab annually if stable • Neck ultrasound annually for 5 years, and then less often if imaging and Tg measurement and Tg ab stable • See NCCN Guidelines for Survivorship	→ Recurrent Disease (PAP-9) or Metastatic Disease (PAP-10)

[k] Principles of TSH Suppression (THYR-A).
[ee] 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.
[ff] Interpretation of rising or new Tg ab is assay dependent and best performed as a radioimmunoassay and with a consistent assay for interpretation of trends.

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

RECURRENT DISEASE

- Rising or newly elevated Tg and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[gg]

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

Locoregional recurrence → Consider iodine total body scan →

Surgery (preferred) if resectable[ii]
and
Consider RAI therapy,[hh] if preoperative or postoperative radioiodine imaging positive
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:
- RT[q]
  and/or
- Systemic therapies (Treatment [PAP-10])

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[q]
and/or
Local therapies when available[jj]
and/or
If RAI-refractory, see Treatment (PAP-10)

[k] Principles of TSH Suppression (THYR-A).
[q] Principles of Radiation and RAI Therapy (THYR-C).
[gg] 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 months 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 used 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 Tg levels.
[hh] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[ii] Preoperative vocal cord assessment, if central neck recurrence.
[jj] Ethanol ablation, cryoablation, RFA, etc.

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

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC RAI-REFRACTORY DISEASE

Structurally persistent/recurrent locoregional or distant metastatic RAI-refractory disease →

- **For advanced, progressive, or threatening disease, somatic testing to identify actionable mutations (including *ALK, NTRK, BRAF*, and *RET* gene fusions), mismatch repair deficiency (dMMR), microsatellite instability (MSI), and tumor mutational burden (TMB)**
- **Brain imaging (CT or MRI) with contrast for CNS symptoms or prior to starting systemic therapy**

→ **Unresectable locoregional recurrent/persistent disease**

→ **Soft tissue metastases (eg, lung, liver, muscle) excluding central nervous system (CNS) metastases (see below)**

→ (for both of the above)

- **Consider clinical trial**
- **Continue to suppress TSH with levothyroxine[l]**
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Consider resection of distant metastases and/or RT[q] or other local therapies[jj] when available to metastatic lesions if progressive and/or symptomatic (Treatment of Locoregional Recurrence [PAP-9])**
- **Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[kk] (PAP-7)**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

→ **Bone Metastases (PAP-11)**

→ **CNS Metastases (PAP-12)**

[l] Principles of TSH Suppression (THYR-A).
[q] Principles of Radiation and RAI Therapy (THYR-C).
[jj] Ethanol ablation, cryoablation, RFA, etc.
[kk] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).

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

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE [ll]

Bone metastases →

- **Consider surgical palliation and/or RT[q]/other local therapies[jj] 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/RT in select cases**
- **Consider intravenous bisphosphonate or denosumab[mm]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[kk] (PAP-7)**
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

[q] Principles of Radiation and RAI Therapy (THYR-C).
[jj] Ethanol ablation, cryoablation, RFA, etc.
[kk] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[ll] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[mm] 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. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery (SRS)[q] is preferred or**
- **For multiple CNS lesions, consider radiotherapy, including whole brain radiotherapy RT (WBRT) or SRS,[q] and/or resection in select cases**
  and/or
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

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

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

FNA RESULTS | **DIAGNOSTIC PROCEDURES** | **PRIMARY TREATMENT**

Follicular neoplasm[a] (Bethesda IV) (THYR-1) →

Diagnostic procedures:
- Thyroid and neck ultrasound (including central and lateral cervical nodal compartments), if not previously done
- Consider CT/MRI with contrast for locally advanced disease or vocal cord paresis[b]
- Consider assessment of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)[c]
- Screen for personal and/or family history suggestive of inherited cancer risk[i]

→ **Primary treatment:**

- Total thyroidectomy if radiographic evidence or intraoperative findings of extrathyroidal extension or patient preference
- Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease
  - → Benign or NIFTP[e] → Levothyroxine therapy to keep TSH normal[f]
  - → Papillary Carcinoma (PAP-3)
  - → Follicular carcinoma → Postsurgical Evaluation (FOLL-2)

or

Lobectomy/isthmusectomy
- → Invasive cancer (widely invasive or encapsulated angioinvasive[h] with ≥4 vessels) → Completion of thyroidectomy → Postsurgical Evaluation (FOLL-2)
- → Encapsulated angioinvasive[h] with <4 vessels or Minimally invasive follicular thyroid carcinoma (FTC)[d] →
  - Completion of thyroidectomy[g] → Postsurgical Evaluation (FOLL-2)
  - or Disease monitoring →
    - Consider levothyroxine therapy to keep TSH low or normal[f]
    - Disease Monitoring and Management (FOLL-6)
- → Benign or NIFTP[e] → Disease monitoring →
  - Consider levothyroxine therapy to keep TSH low or normal[f]
  - Disease Monitoring and Management (FOLL-6)
- → Papillary Carcinoma (PAP-3)

Footnotes on FOLL-1A

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

FOOTNOTES

[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) 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 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] 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.
[h] Blood vessel invasion fewer than 4 vessels does not require completion thyroidectomy.
[i] Principles of Cancer Risk Assessment and Counseling (THYR-E).

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

POSTSURGICAL EVALUATION

No gross residual disease in neck → Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (FOLL-3)

Gross residual disease in neck → Cross-sectional CT or MRI of neck with contrast →

- **Resectable** → Resect, if possible →
  - No gross residual disease → Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (FOLL-3)
  - Gross residual disease → (see below)
- **Unresectable**[j] (and gross residual disease after resection) →
  - TSH + Tg measurement + Tg ab (6–12 weeks postoperatively)
  - Iodine-123 or iodine-131[l] total body radioiodine imaging (category 2B)
  - →
    - RAI uptake absent[n] → Monitoring of residual disease or Consider EBRT if disease is threatening vital structures[k] or Consider RAI therapy[k]
    - RAI uptake present[m] or No RAI imaging performed →
      - RAI therapy (preferred)[k]
      - TSH-stimulated Tg
      - Consider EBRT[k]
- **Unresectable**[j] → For locoregional invasive disease or rapid progression, consider EBRT, or systemic therapy[k] →
  - TSH + Tg measurement + Tg ab (6–12 weeks postoperatively)
  - Iodine-123 or iodine-131[l] total body radioiodine imaging (category 2B)
  - →
    - RAI uptake absent[n] → Monitoring of residual disease or Consider RAI therapy[k] or Consider systemic therapy (FOLL-9)
    - RAI uptake present[m] or No RAI imaging performed →
      - RAI therapy (preferred)[k]
      - TSH-stimulated Tg

All of the above →
- Suppress TSH with levothyroxine[f]
- Disease Monitoring and Management (FOLL-6)

[f] 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] Principles of Radiation and RAI Therapy (THYR-C).
[l] If considering dosimetry iodine-131 is the preferred agent.
[m] If higher than expected uptake (residual thyroid uptake or distant metastasis), change dose accordingly.
[n] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.

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

CLINICOPATHOLOGIC FACTORS	CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY	
RAI not typically recommended (if all present): • Largest primary tumor ≤2 cm • Intrathyroidal • No vascular invasion • Clinical N0 • No detectable Tg ab • Postoperative unstimulated Tg <1 ng/mL[o] • Negative postoperative ultrasound, if done[p]	→	RAI not typically indicated (FOLL-6)
RAI selectively recommended (if any present): • Large primary tumor size[u] • Minor vascular invasion (<4 foci) • Cervical lymph node metastases (millimetric central nodes)[t] • Postoperative unstimulated Tg 1–10 ng/mL[o] • Microscopic positive margins	→ RAI is recommended when the combination of individual clinical factors (such as the extent 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 (FOLL-4)
RAI recommended (if any present): • Differentiated high-grade carcinoma[s] • Significant N1b disease • Gross extrathyroidal extension[q] • Extensive vascular invasion (≥4 foci) • Postoperative unstimulated Tg >10 ng/mL[o,r] • Bulky or >5 positive lymph nodes[t]	→	RAI Being Considered (FOLL-4)
Known or suspected distant metastases at presentation	→	Amenable to RAI (FOLL-5)
Gross Residual RAI-refractory Disease	→	(FOLL-9)

[o] Tg values obtained 6–12 weeks after total thyroidectomy.
[p] If preoperative imaging incomplete, postoperative imaging should evaluate central and lateral neck.
[q] Minimal extrathyroidal extension alone likely does not warrant RAI. This is seen by the surgeon during thyroid resection.
[r] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT [with contrast if there is concern about mediastinal lymph node metastases]) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.
[s] Differentiated high-grade carcinoma includes follicular thyroid carcinoma with ≥5 mitoses per 2 mm^2 and/or tumor necrosis. There is a lack of data regarding benefit of RAI in isolation with these features.
[t] Consider evaluation for follicular variant of PTC if cervical lymph node involvement is present
[u] There are no data for a specific size cut-off; >4 cm may be considered, although data are conflicting.

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

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

RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → Clinicopathologic findings prompting consideration for RAI, without gross residual disease or known distant metastasis (FOLL-3)

- → RAI therapy indicated based on pathology → Consider pretreatment neck imaging[m,n,v] → Resect clinically significant structural disease if possible → • RAI therapy for remnant ablation or adjuvant therapy[k] → Disease Monitoring and Management (FOLL-6) Levothyroxine to appropriate TSH target (THYR-A)
- → RAI therapy not indicated based on pathology → Disease Monitoring and Management (FOLL-6) Levothyroxine to appropriate TSH target (THYR-A)

[k] Principles of Radiation and RAI Therapy (THYR-C).
[m] If higher than expected uptake (residual thyroid uptake or distant metastasis), change dose accordingly.
[n] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
[v] 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. Patients on dialysis require special handling.

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

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

6–12 weeks post-thyroidectomy → **Known or suspected distant metastases at presentation or elevated Tg (FOLL-3)** →

- **Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci[w,y]**
- **Resect clinically significant structural disease if possible**

→ **At least 4–6 weeks following imaging[x]:**
- **Consider pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with TSH stimulation[k,v]**

→ **Confirmed radioiodine-avid tumor or Thyroid remnant uptake only** →
- **RAI therapy[k]**
- **Consider other local therapies (EBRT,[k] etc) as primary therapy or postoperative for symptomatic structural metastatic disease**

→ **No uptake or not performed** →
- **Consider RAI adjuvant therapy[k]**
  Consider other local therapies (EBRT,[k] etc) as primary therapy or postoperative for symptomatic structural metastatic disease

→
- **Disease Monitoring and Management (FOLL-6)**
- **Levothyroxine to appropriate TSH target (THYR-A)**

[k] Principles of Radiation and RAI Therapy (THYR-C).
[v] 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. Patients on dialysis require special handling.
[w] To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or EBRT) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.
[x] Consider 24-hour urine iodine.
[y] If suspicion of pulmonary metastasis, chest CT can be done without contrast.

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

TREATMENT	DISEASE MONITORING	FINDINGS	MANAGEMENT	
Lobectomy	• Physical examination • TSH • Neck ultrasound at 6–12 months	Abnormal contralateral nodule or lymph node	Biopsy of suspicious areas (if lymph node, consider Tg washout)	Postsurgical Evaluation (FOLL-2)
		No evidence of disease	• Physical examination • Neck ultrasound as clinically indicated[z] See NCCN Guidelines for Survivorship	Recurrent Disease (FOLL-8) or Metastatic Disease (FOLL-9)
Total thyroidectomy without RAI	• Physical examination • TSH • Tg measurement and Tg ab at 6–12 weeks • Neck ultrasound at 6–12 months	Rising or new Tg ab	Consider additional imaging (CT neck/chest), PET, or RAI imaging	Recurrent Disease (FOLL-8)
		Abnormal imaging and/or rising Tg	Biopsy of suspicious areas on imaging (consider Tg washout)	Recurrent Disease (FOLL-8)
		No evidence of disease	• Physical examination • TSH (goal based on risk stratification) • Tg measurement and Tg ab annually if stable • Neck ultrasound as clinically indicated[z] • See NCCN Guidelines for Survivorship	Recurrent Disease (FOLL-8) or Metastatic Disease (FOLL-9)

Total thyroidectomy with RAI (FOLL-7)

[z] Follicular thyroid carcinoma does not spread to lymph nodes; however, could spread to soft tissue within the neck.

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

TREATMENT	DISEASE MONITORING	FINDINGS	MANAGEMENT	
Total thyroidectomy with RAI →	• Physical examination • Neck ultrasound at 6–12 months • TSH • Tg measurement and Tg ab[aa]	Rising or new Tg ab[bb] →	Consider additional imaging (CT neck/chest), PET, or RAI imaging	→ Recurrent Disease (FOLL-8)
		Abnormal imaging and/or rising Tg →	• Consider biopsy of suspicious areas on imaging (consider Tg washout) • Follow-up imaging of known iodine-avid disease with cross-sectional imaging (CT or MRI)	→ Recurrent Disease (FOLL-8)
		No evidence of disease →	• Physical examination • TSH[f] • Tg measurement and Tg ab annually if stable • Neck ultrasound annually for 5 years, and then less often if imaging and Tg measurement and Tg ab stable • See NCCN Guidelines for Survivorship	→ Recurrent Disease (FOLL-8) or Metastatic Disease (FOLL-9)

[f] Principles of TSH Suppression (THYR-A).
[aa] 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.
[bb] Interpretation of rising or new Tg ab is assay dependent and best performed as a radioimmunoassay and with a consistent assay for interpretation of trends.

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

RECURRENT DISEASE

- Rising or newly elevated Tg and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[dd]

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

Locoregional recurrence → Consider iodine total body scan →

Surgery (preferred) if resectable[cc]
and
Consider RAI therapy,[ee] if preoperative or postoperative 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:
- RT[k]
  and/or
- Systemic therapies (Treatment [FOLL-9])

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[k]
and/or
Local therapies when available[ff]
and/or
If RAI-refractory, see Treatment (FOLL-9)

[f] Principles of TSH Suppression (THYR-A).
[k] Principles of Radiation and RAI Therapy (THYR-C).
[cc] Preoperative vocal cord assessment, if central neck recurrence.
[dd] 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 months 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 used 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 Tg levels.
[ee] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.

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

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC RAI-REFRACTORY DISEASE

Structurally persistent/recurrent locoregional or distant metastatic RAI-refractory disease

→

- **For advanced, progressive, or threatening disease, somatic testing to identify actionable mutations (including *ALK*, *NTRK*, *BRAF*, and *RET* gene fusions),[hh] dMMR, MSI, and TMB**
- **Brain imaging (CT or MRI) with contrast for CNS symptoms or prior to starting systemic therapy**

→ **Unresectable locoregional recurrent/ persistent disease**

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

→

- **Consider clinical trial**
- **Consider systemic therapy for progressive and/ or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Continue to suppress TSH with levothyroxine[f]**
- **Consider resection of distant metastases and/or EBRT[k] or other local therapies[ff] when available to metastatic lesions if progressive and/or symptomatic (Treatment of Locoregional Recurrence [FOLL-8])**
- **Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[w] (FOLL-6)**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

→ **Bone metastases (FOLL-10)**

→ **CNS metastases (FOLL-11)**

[f] Principles of TSH Suppression (THYR-A).
[k] Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[hh] *BRAF* V600E mutation in follicular carcinoma is rare. If this mutation is present in a case of follicular carcinoma, pathology diagnosis should be questioned.

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

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE [ii]

Bone metastases →

- **Consider surgical palliation and/or RT[k]/other local therapies[ff] 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/RT in select cases**
- **Consider intravenous bisphosphonate or denosumab[jj]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[gg] (FOLL-6)**
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

[k] Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[ii] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[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. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or SRS is preferred**
  or
- **For multiple CNS lesions, consider radiotherapy, including WBRT or SRS[k], and/or resection in select cases**
  and/or
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

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

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

FNA RESULTS | **DIAGNOSTIC PROCEDURES** | **PRIMARY TREATMENT**

Oncocytic follicular neoplasm[a] (Bethesda IV) THYR-1 →

- Assess for signs of malignancy
  - Thyroid and neck ultrasound (including central and lateral cervical nodal compartments), if not previously done
  - Consider molecular diagnostics[a]
  - Screen for personal and/or family history suggestive of inherited cancer risk[b]

→ **Any concerning features**
- → **Evidence of locoregional spread (ETE, nodal disease)** → • Consider neck CT[c] • Total thyroidectomy and therapeutic neck dissection → **Postsurgical Evaluation (ONC-2)**
- → **No evidence of locoregional spread** → • Lobectomy or total thyroidectomy (lobectomy may be preferred for smaller tumor)
  - → **Invasive cancer (widely invasive or encapsulated angioinvasive[d] with ≥4 vessels)** → Completion of thyroidectomy → **Postsurgical Evaluation (ONC-2)**
  - → **Encapsulated angioinvasive[d] with <4 vessels or Minimally invasive oncocytic carcinoma[e]** → Disease monitoring (preferred)[f] → • Consider levothyroxine therapy to keep TSH low or normal[g] • Disease Monitoring and Maintenance (ONC-6)
  - → **Benign** → Disease monitoring → • Consider levothyroxine therapy to keep TSH low or normal[g] • Disease Monitoring and Maintenance (ONC-6)

→ **All features reassuring, including molecular genetics** → Observe

[a] The diagnosis of oncocytic carcinoma, formerly known as Hurthle cell carcinoma, requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.
[b] Principles of Cancer Risk Assessment and Counseling (THYR-E).
[c] Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in RAI treatment will not cause harm.
[d] Blood vessel invasion fewer than four vessels does not require completion thyroidectomy.
[e] Minimally invasive oncocytic carcinoma is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.
[f] Disease monitoring is preferred in most circumstances. However, there are certain clinical scenarios in which completion of thyroidectomy may be appropriate.
[g] Principles of TSH Suppression (THYR-A).

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

POSTSURGICAL EVALUATION

No gross residual disease in neck → Consideration for Initial Postoperative RAI Therapy (ONC-3)

Gross residual disease in neck →
- Cross-sectional CT or MRI of neck with contrast
- FDG-PET/CT or FDG-PET/MRI

→ **Resectable** → Resect, if possible
- → No gross residual disease → Consideration for Initial Postoperative RAI Therapy (ONC-3)
- → Gross residual disease → see below (TSH + Tg measurement)

→ **Unresectable[j] noninvasive and not metastatic** →
- TSH + Tg measurement + Tg ab (6–12 weeks postoperatively)
- Iodine-123 or iodine-131[k] total body radioiodine imaging (category 2B)

→ RAI uptake absent[h,i] → Monitoring of residual disease or Consider EBRT if disease is threatening vital structures[h]

→ RAI uptake present[h] or No RAI imaging performed →
- RAI therapy (preferred)[h]
- Consider EBRT[h] if disease is threatening vital structures

→ **Unresectable invasive or widely metastatic** → For locoregional invasive disease or rapid progression, consider EBRT, systemic therapy[h] →
- TSH + Tg measurement + Tg ab (6–12 weeks postoperatively)
- Iodine-123 or iodine-131[k] total body radioiodine imaging (category 2B)

→ RAI uptake present[h] or No RAI imaging performed → RAI therapy[h]

→ RAI uptake absent[h,i] → Treatment of Locally Recurrent, Advanced, and/or Metastatic Disease (ONC-9)

→ Heterogeneous uptake (ie, some but not all known disease has iodine uptake) → Treatment of Locally Recurrent, Advanced, and/or Metastatic Disease (ONC-9) or Consider RAI when majority of disease is RAI avid[h]

Footnotes on ONC-2A

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

POSTSURGICAL EVALUATION - FOOTNOTES

[h] Principles of Radiation and RAI Therapy (THYR-C).
[i] A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.
[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.

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

CLINICOPATHOLOGIC FACTORS[l]

CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

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

→ RAI not typically indicated (ONC-6)

RAI selectively recommended:
- Large primary tumor size[o]
- Minor vascular invasion(<4 foci)
- Cervical lymph node metastases (millimetric central nodes)
- Postoperative unstimulated Tg 1–10 ng/mL[m]
- Microscopic positive margins

→ RAI is recommended when the combination of individual clinical factors (such as the extent 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 (ONC-4)

RAI recommended (if any present):
- Differentiated high-grade carcinoma[p]
- Significant N1b disease
- Gross extrathyroidal extension[q]
- Extensive vascular invasion (≥4 foci)
- Postoperative unstimulated Tg >10 ng/mL[m,r]
- Bulky or >5 positive lymph nodes

→ RAI being considered (ONC-4)

Known or suspected distant metastases at presentation → Amenable to RAI (ONC-5)

Gross residual disease → ONC-9

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

[l] A majority of oncocytic carcinoma are non–iodine-avid.
[m] Tg values obtained 6–12 weeks after total thyroidectomy.
[n] If preoperative imaging incomplete, postoperative imaging should evaluate central and lateral neck.
[o] There are no data for a specific size cut-off; >4 cm may be considered, although data are conflicting.
[p] Differentiated high-grade carcinoma includes oncocytic carcinoma with ≥5 mitoses per 2 mm^2 and/or tumor necrosis.
[q] Minimal extrathyroidal extension alone likely does not warrant RAI. This is seen by the surgeon during thyroid resection.
[r] Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT [with contrast if there is concern about mediastinal lymph node metastases]) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

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

RAI PLANNING AFTER TOTAL THYROIDECTOMY

RAI planned

- **No gross residual disease**
  - **Low Tg** → **Iodine 131 therapy (ONC-3) or disease monitoring (ONC-6)**
  - **• High Tg • Negative neck imaging** → **CT chest without contrast or PET**
    - **Negative imaging** → **Diagnostic whole body scan (Iodine 131 or iodine 123) and consider empiric dosing of RAI[h]** → **(ONC-6)**
    - **Distant metastases present** → **Known or suspected metastatic disease (ONC-5)**
- **Gross unresectable disease or distant metastases suspected** → **Known or suspected metastatic disease (ONC-5)**
- **Gross resectable disease** → **Resect clinically significant structural disease if possible[s]** → **RAI planned**

[h] Principles of Radiation and RAI Therapy (THYR-C).
[s] Weigh the risks and benefits of nerve entry.

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

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

Known or suspected distant metastases at presentation or elevated Tg (ONC-3)

→

- **Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci[t,u]**
- **Resect clinically significant structural disease if possible**

→

- **Consider RAI adjuvant therapy with or without pretreatment iodine scan[h,v] Consider other local therapies (EBRT,[h] etc) as primary therapy or postoperative for symptomatic structural metastatic disease**

→

- **Disease Monitoring and Maintenance (ONC-6)**
- **Levothyroxine to appropriate target (THYR-A)**

[h] Principles of Radiation and RAI Therapy (THYR-C)
[t] To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or EBRT) to prevent invasion/compression.
[u] If suspicion of pulmonary metastasis, chest CT can be done without contrast.
[v] 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. Patients on dialysis require special handling.

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

TREATMENT	DISEASE MONITORING	FINDINGS	MANAGEMENT	
Lobectomy	• Physical examination • TSH • Neck ultrasound at 6–12 months	Abnormal contralateral nodule or lymph node	Biopsy of suspicious areas (if lymph node, consider Tg washout)	Postsurgical Evaluation (ONC-2)
		No evidence of disease	• Physical examination • Neck ultrasound as clinically indicated See NCCN Guidelines for Survivorship	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
Total thyroidectomy without RAI	• Physical examination • TSH • Tg measurement and Tg ab at 6–12 weeks • Neck ultrasound at 6–12 months	Rising or new Tg ab	Consider additional imaging (CT neck/chest), PET, or RAI imaging	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
		Abnormal imaging and/or rising Tg	Biopsy of suspicious areas on imaging (consider Tg washout)	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
		No evidence of disease	• Physical examination • TSH (goal based on risk stratification) • Tg measurement and Tg ab annually if stable • Neck ultrasound as clinically indicated • See NCCN Guidelines for Survivorship	Recurrent Disease (ONC-8)

Total thyroidectomy with RAI (ONC-7)

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

TREATMENT | DISEASE MONITORING | FINDINGS | MANAGEMENT

Total thyroidectomy with RAI

→ **RAI uptake present on post-therapy scan** → Disease monitoring:
- Physical examination
- Neck ultrasound at 6–12 months
- TSH
- Tg measurement and Tg ab[w]
- Follow-up imaging of known iodine-avid disease with cross-sectional imaging (CT or MRI)

FINDINGS	MANAGEMENT	
Rising Tg or new or rising Tg ab[x]	Consider additional imaging (CT neck/chest), PET, or RAI imaging	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
Abnormal imaging	Consider biopsy of suspicious areas on imaging (consider Tg washout)	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
No evidence of disease	• Physical examination • TSH[g] • Tg measurement and Tg ab annually if stable • Neck ultrasound annually for 5 years, and then less often if imaging and Tg measurement and Tg ab stable • See NCCN Guidelines for Survivorship	Recurrent Disease (ONC-8)

→ **RAI uptake absent on post-therapy scan** → Disease monitoring:
- Physical examination
- Neck ultrasound at 6–12 months
- TSH
- Tg measurement and Tg ab

FINDINGS	MANAGEMENT	
Rising Tg or new or rising Tg ab[x]	Consider additional imaging (CT neck/chest), or PET	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
Abnormal imaging	Consider biopsy of suspicious areas on imaging (consider Tg washout)	Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)
No evidence of disease	• Physical examination • TSH[g] • Tg measurement and Tg ab annually if stable • Neck ultrasound annually for 5 years, and then less often if imaging and Tg measurement and Tg ab stable • See NCCN Guidelines for Survivorship	Recurrent Disease (ONC-8)

[g] Principles of TSH Suppression (THYR-A).
[w] 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.
[x] Interpretation of rising or new Tg ab is assay dependent and best performed as a radioimmunoassay and with a consistent assay for interpretation of trends.

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

RECURRENT DISEASE

- Rising or newly elevated Tg or Tg ab and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[y]

→ Suppress TSH with levothyroxine[g] → Continue surveillance with Tg, ultrasound, and other imaging as clinically indicated (ONC-6)

Locoregional recurrence → Consider iodine total body scan →

Surgery (preferred) if resectable[z]
and
Consider RAI therapy[aa], if preoperative or postoperative 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:
- RT[h]
  and/or
- Systemic therapies (Treatment [ONC-9])

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[h] and/or
Local therapies when available[bb]
and/or
Treatment (ONC-9)

[g] Principles of TSH Suppression (THYR-A).
[h] Principles of Radiation and RAI Therapy (THYR-C).
[z] Preoperative vocal cord assessment, if central neck recurrence.
[y] 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 months 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 used 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 Tg levels.
[aa] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[bb] Ethanol ablation, cryoablation, RFA, etc.

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

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE

Structurally persistent/ recurrent locoregional or distant metastatic disease →

- **For advanced, progressive, or threatening disease, somatic testing to identify actionable mutations (including *ALK, NTRK, BRAF,* and *RET* gene fusions), dMMR, MSI, and TMB**
- **If low volume, not rapidly progressing disease, consider evaluation for RAI avidity**
- **Brain imaging (CT or MRI) with contrast for CNS symptoms or prior to starting systemic therapy**

→ **Unresectable locoregional recurrent/ persistent disease** or **Soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)** →

- **Consider clinical trial**
- **Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[cc] (ONC-6)**
- **Continue to suppress TSH with levothyroxine[g]**
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Consider resection of distant metastases and/or RT[h] or other local therapies[bb] when available to metastatic lesions if progressive and/or symptomatic (Treatment of Locoregional Recurrence [ONC-8])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

→ **Bone metastases (ONC-10)**

→ **CNS metastases (ONC-11)**

[g] Principles of TSH Suppression (THYR-A).
[h] Principles of Radiation and RAI Therapy (THYR-C).
[bb] Ethanol ablation, cryoablation, RFA, etc.
[cc] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).

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

TREATMENT OF METASTATIC DISEASE

Bone metastases →

- **Consider surgical palliation and/or RT[h]/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/RT in select cases**
- **Consider intravenous bisphosphonate or denosumab[dd]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[cc] (ONC-6)**
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

[h] Principles of Radiation and RAI Therapy (THYR-C).
[bb] Ethanol ablation, cryoablation, RFA, etc.
[cc] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[dd] 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. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

TREATMENT OF METASTATIC DISEASE

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or SRS[h] is preferred**
  or
- **For multiple CNS lesions, consider radiotherapy, including WBRT or SRS,[h] and/or resection in select cases**
- **Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

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

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

CLINICAL PRESENTATION	DIAGNOSTIC PROCEDURES	PRIMARY TREATMENT	
Medullary thyroid carcinoma on FNA by cytology or molecular diagnostics[h] →	• Basal serum calcitonin level • Carcinoembryonic antigen (CEA) • Pheochromocytoma screening[b] • Serum calcium • Screen for germline *RET* PV[c] (exons 8, 10, 11, 13–16); genetic counseling may be indicated[f] • Thyroid and neck ultrasound (including central and lateral cervical nodal 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 for metastatic disease: ▸ Consider if calcitonin is >300 pg/mL, 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 whole body MRI	→ • Total thyroidectomy with 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 • Lobectomy can be considered in select cases without germline *RET* mutation if no concerns for abnormal adenopathy and contralateral nodules • Consider therapeutic EBRT[g] for grossly incomplete tumor resection only when additional attempts at surgical resection have been ruled out • Adjuvant EBRT is rarely recommended[g] • Postoperative administration of levothyroxine to normalize TSH	Management 2–3 Months Postoperative (MEDU-5)

Medullary thyroid carcinoma diagnosed after initial thyroid surgery → Additional Workup and Management (MEDU-2)

Germline mutation of *RET* pathologic variant (PV)[a,b] → 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 in patients for whom results from *RET* PV testing have not yet been received. See NCCN Guidelines for Neuroendocrine and Adrenal Tumors.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling. See Principles of Cancer Risk Assessment and Counseling (THYR-E).
[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] Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor. Surgical intervention should not be delayed while awaiting test results. See Principles of Cancer Risk Assessment and Counseling (THYR-E).
[g] Principles of Radiation and RAI Therapy (THYR-C).
[h] High-grade pathologic features include tumor necrosis and an elevated mitotic count or Ki67 proliferation index.

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

CLINICAL PRESENTATION → **ADDITIONAL WORKUP** → **MANAGEMENT**

Medullary thyroid carcinoma diagnosed after initial thyroid surgery[i]

→

- **Basal serum calcitonin level**
- **CEA**
- **Screen for germline *RET* PV[c,j] (exons 10, 11, 13–16); genetic counseling may be indicated**
- **Central and lateral cervical nodal compartments ultrasound, if not previously done**

→ **Germline *RET* PV identified** → **Additional Workup and Primary Treatment (MEDU-3)**

→ **Germline *RET* PV not identified** → **Management 2–3 Months Postoperative (MEDU-5)**

[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling. See Principles of Cancer Risk Assessment and Counseling (THYR-E).
[i] 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* PV or radiographic evidence of disease (ie, biopsy-proven residual neck disease).
[j] Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.

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

CLINICAL PRESENTATION		ADDITIONAL WORKUP	PRIMARY TREATMENT	
Germline *RET* PV[a,c]	Multiple endocrine neoplasia (MEN2B) (*RET* PV)[k]	• Basal serum calcitonin level[l] • CEA • Pheochromocytoma screening[b,m] • Central and lateral cervical nodal compartments ultrasound,[n] if not previously done • Consider neck CT with contrast if indicated	• Total thyroidectomy during childhood or at diagnosis[a] • Surgery is recommended during the first year of life for patients with codon M918T mutations • Surgery is recommended before age 5 for patients with codon A883F mutations • Therapeutic neck dissectionguided by imagingConsider prophylactic central neck dissection (level VI) • Postoperative administration of levothyroxine to normalize TSH	Management 2–3 Months Postoperative (MEDU-5)
	MEN2A/Familial medullary thyroid carcinoma (FMTC) (*RET* PV)[k]	• See Additional Workup above • Serum calcium + parathyroid hormone[n]		Primary Treatment (MEDU-4)

[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 in patients for whom results from *RET* PV testing have not yet been received. See NCCN Guidelines for Neuroendocrine and Adrenal Tumors.

[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling. See Principles of Cancer Risk Assessment and Counseling (THYR-E).

[k] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* PV. 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 most other *RET* PVs associated with MEN2A or FMTC are generally moderate risk. Codon V804M mutations are common but carry a low lifetime risk of MTC (~4%). Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* PVs 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 Jr, et al. Thyroid 2015;25:567-610.)

[l] Normal calcitonin ranges have not been established for very young children.

[m] Screening for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A) should be performed annually. For some *RET* PVs (codons 768, 790, 804, or 891), less frequent screening may be appropriate.

[n] In addition to ultrasound, parathyroid imaging may include sestamibi scan with SPECT or 4D-CT depending on institutional practice/protocol. If testing indicates hyperparathyroidism, parathyroid imaging is clinically indicated in addition to ultrasound.

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

CLINICAL PRESENTATION

PRIMARY TREATMENT

MEN2A/FMTC (*RET* PV)[a,c,k]

No primary hyperparathyroidism →

- **Management based on codon mutation**
  - **High risk (codon 634 mutations): Surgery before age 5 based on serum calcitonin levels**
  - **Moderate risk (all other PVs): Prophylactic thyroidectomy may be delayed, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, and there is no history of aggressive MTC in the family**
  - **Low risk (codon V804M mutations): Given the low penetrance of MTC in these patients (~4%), surveillance may be a viable long-term strategy in the absence of a strong family history of MTC**

→ **Surgery chosen** → **Total thyroidectomy and dissection of lymph node compartments based on ultrasound findings and preoperative serum calcitonin levels**[o] → **Management 2–3 Months Postoperative (MEDU-5)**

→ **Surveillance chosen** → **Surveillance with annual serum calcitonin measurement and ultrasound**

Primary hyperparathyroidism →

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

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

[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. See Principles of Cancer Risk Assessment and Counseling (THYR-E).

[k] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* PV. 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 most other *RET* PVs associated with MEN2A or FMTC are generally moderate risk. Codon V804M mutations are common but carry a low lifetime risk of MTC (~4%). Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* PVs 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 Jr, et al. Thyroid 2015;25:567-610.)

[o] 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.

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

MANAGEMENT 2–3 MONTHS POSTOPERATIVE

DISEASE MONITORING[q]

- Basal calcitonin
- CEA

→ **Detectable basal calcitonin or Elevated CEA[t]**

→
- Neck ultrasound
- If calcitonin ≥150 pg/mL, CT or MRI with contrast of neck, liver, and chest
- Consider whole body MRI in patients with very elevated calcitonin levels[u]

→ **Imaging positive or symptomatic disease** → Recurrent or Persistent Disease (MEDU-6 and MEDU-7)

→ **Imaging negative and asymptomatic** →
- Serum calcitonin, CEA every 6–12 mo
- Additional studies or more frequent testing based on calcitonin/CEA doubling time[s]
  - FDG-PET/CT or Ga-68 DOTATATE or MRI with contrast of the neck, chest, abdomen with liver protocol
- No additional imaging required if calcitonin and CEA stable

→ Positive result → Recurrent or Persistent Disease (MEDU-6 and MEDU-7)

→ Negative result → Continue disease monitoring or Consider cervical reoperation, if primary surgery incomplete → (return to Neck ultrasound / imaging above)

→ **Basal calcitonin undetectable and CEA within reference range[p]** → Disease monitoring →
- Annual serum calcitonin, CEA
- Consider central and lateral neck compartments ultrasound
- Additional studies or more frequent testing if significantly rising calcitonin or CEA[s]
- No additional imaging required if calcitonin and CEA stable
- For MEN2B or MEN2A, annual biochemical screenings for pheochromocytoma and hyperparathyroidism (MEN2A)[r]

→ Positive result → Recurrent or Persistent Disease (MEDU-6 and MEDU-7)

→ Negative result → Continue disease monitoring → (return to Neck ultrasound / imaging above)

[p] The likelihood of significant residual disease with an undetectable basal calcitonin is very low.
[q] See NCCN Guidelines for Survivorship.
[r] Page PHEO-1 from the NCCN Guidelines for Neuroendocrine and Adrenal Tumors.
[s] It is unlikely that there will be radiographic evidence of disease when calcitonin is less than 150 pg/mL.
[t] Imaging may be indicated based on high burden of disease, calcitonin >500 pg/mL, or elevated CEA levels.
[u] The ATA Guidelines recommend T/L spine and pelvis MRI. Wells SA, et al. Thyroid 2015;25:567-610.

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

RECURRENT OR PERSISTENT LOCOREGIONAL DISEASE		TREATMENT	
Locoregional →	Somatic testing[w] →	• Surgical resection is the preferred treatment modality • EBRT should only be considered for unresectable disease not amenable to targeted systemic therapy, or less commonly, after surgical resection[g] • Consider systemic therapy[v] for unresectable disease that is symptomatic or progressing by RECIST criteria (Principles of Systemic Therapy [THYR-B]). • Disease monitoring	→ Recurrent or Persistent Disease; Distant Metastases (MEDU-7)

[g] Principles of Radiation and RAI Therapy (THYR-C).
[v] Increasing tumor markers (eg, calcitonin/CEA), in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[w] Somatic testing including TMB or RET somatic genotyping in patients who are germline wild-type or germline unknown.

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

RECURRENT OR PERSISTENT DISEASE
DISTANT METASTASES

Asymptomatic disease → **Somatic testing[w]** →
- **Disease monitoring**
- **Consider resection (if possible) Systemic therapy[v] if not resectable and progressing by RECIST criteria (Principles of Systemic Therapy [THYR-B])**

→ **Progressive disease, pathway below**

Symptomatic disease or Progression[v] → **Somatic testing[w]** →
- **Systemic therapy (Principles of Systemic Therapy [THYR-B]) or clinical trial**
- **EBRT for local symptoms[g]**
- **Consider intravenous bisphosphonate or denosumab[x] therapy for bone metastases**
- **Consider palliative resection, ablation (eg, RFA, embolization, other regional therapy), or other regional treatment**
- **Best supportive care, see NCCN Guidelines for Palliative Care**

[g] Principles of Radiation and RAI Therapy (THYR-C).
[v] Increasing tumor markers (eg, calcitonin/CEA), in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[w] Somatic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.
[x] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk. An FDA- approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

FNA OR CORE BIOPSY FINDING[a]

Anaplastic thyroid carcinoma (ATC)[a] →

DIAGNOSTIC PROCEDURES

- CBC with differential
- Comprehensive chemistry
- TSH
- Neck ultrasound
- CT with contrast of head, neck, chest, abdomen, pelvis
- Laryngoscopy, including evaluation of vocal cord mobility
- FDG-PET/CT or MRI
- In case of airway invasion, bronchoscopy
- Molecular testing for actionable mutations[b]
- BRAF immunohistochemistry (IHC) testing[b]

→

ESTABLISH GOALS OF THERAPY[c]

- Expedient consultation with multidisciplinary management team
- Discuss prognosis
- Discuss risks/benefits of treatment options
- Discuss palliative care options including airway management

STAGE[d]

→ Stage IVA or IVB[a,c] (locoregional disease) ANAP-2

→ Stage IVC (metastatic disease)[c] ANAP-3

[a] Consider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, and lymphoma.
[b] Molecular testing should include *BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, and tumor mutational burden. BRAF IHC testing is recommended due to faster turnaround compared to genetic testing.
[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] Staging (ST-1).

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

STAGE[d] | **TREATMENT**

Stage IVA or IVB[a,c] (locoregional disease)

- **Resectable (potentially curable with surgery)** → **Neoadjuvant dabrafenib/ trametinib for *BRAF* V600E-mutated disease may be considered (category 2B)** → **Total thyroidectomy with therapeutic lymph node dissection**
  - → **R0/R1 resection[e] achieved (usually as incidentally discovered, very small ATC)** → **Adjuvant EBRT[f] with radiosensitizing chemotherapy (Principles of Systemic Therapy [THYR-B]) when clinically appropriate** → **Disease Monitoring and Management (ANAP-3)**
  - → **Incomplete (R2 resection)** → **EBRT[f] with chemotherapy (Principles of Systemic Therapy [THYR-B]) when clinically appropriate** → **Disease Monitoring and Management (ANAP-3)**
- **Unresectable[e] or borderline resectable** → **Consider targeted neoadjuvant therapy[b] (Principles of Systemic Therapy [THYR-B]) for borderline resectable disease when safe to do so or EBRT[f] with chemotherapy (Principles of Systemic Therapy [THYR-B]) when clinically appropriate** → **Surgery can be reconsidered after neoadjuvant therapy depending on response** → **Disease Monitoring and Management (ANAP-3)**

[a] Consider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, and lymphoma.
[b] Molecular testing should include *BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, and tumor mutational burden. BRAF IHC testing is recommended due to faster turnaround compared to genetic testing.
[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] 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] Principles of Radiation and RAI Therapy (THYR-C).

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

METASTATIC DISEASE | **TREATMENT** | **DISEASE MONITORING AND MANAGEMENT**

Stage IVC[d]

→ Aggressive therapy →
- Total thyroidectomy with therapeutic lymph node dissection if resectable (R0/R1)
- Tracheostomy only if strongly indicated ± steroid (avoid prophylactic tracheostomy)
- Locoregional RT
- Systemic therapy ± RT (Principles of Systemic Therapy [THYR-B])
- Molecular testing for actionable mutations if not previously done[b]
- Consider clinical trial

→ Palliative care →
- Palliative locoregional RT
- Local lesion control with surgery or RT (eg, bone,[g] brain metastases)
- Consider tracheostomy
- See NCCN Guidelines for Central Nervous System Cancers
- Best supportive care

→
- Cross-sectional imaging (CT or MRI with contrast) of brain, neck, chest, abdomen, and pelvis at frequent intervals as clinically indicated
- Consider FDG-PET/CT 3–6 months after initial therapy

→
- Continued disease monitoring if no evidence of disease (NED)
- Palliative locoregional RT
- Local lesion control (eg, bone,[g] brain metastases)
- Second-line systemic therapy (Principles of Systemic Therapy [THYR-B]) or clinical trial
- Best supportive care, see NCCN Guidelines for Palliative Care

[b] Molecular testing should include *BRAF, NTRK, ALK*, *RET*, MSI, dMMR, and tumor mutational burden. BRAF IHC testing is recommended due to faster turnaround compared to genetic testing.
[d] Staging (ST-1).
[g] 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. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

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 oncocytic 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**
  - **Patients who are disease free and at low risk for recurrence should have TSH levels maintained at the normal range.**
  - **For patients at low risk for recurrence 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 should have their TSH levels maintained within the reference range.**
  - **Given the potential toxicities associated with TSH-suppressive doses of levothyroxine—including cardiac tachyarrhythmias (especially in the elderly) and bone demineralization (particularly in post-menopausal women) as well as frank symptoms of thyrotoxicosis—the 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 elemental calcium (1200 mg/day) and vitamin D (1000 IU).**

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

PRINCIPLES OF SYSTEMIC THERAPY

Differentiated Thyroid Cancer (RAI-refractory papillary carcinoma, RAI-refractory follicular carcinoma, oncocytic carcinoma): Progressive and/or symptomatic disease		
Preferred regimen	**Other recommended regimen**	**Useful in certain circumstances**
Lenvatinib (category 1)[a,b,c]	Sorafenib (category 1)[a,b,c]	• Cabozantinib if progression after lenvatinib and/or sorafenib (category 1 for papillary carcinoma; category 2A for follicular carcinoma and oncocytic carcinoma) • Dabrafenib/trametinib[e] for *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options • Pembrolizumab/lenvatinib if disease progression on lenvatinib • Pemetrexed/carboplatin if disease progression following prior treatment • *NTRK* gene fusion-positive advanced solid tumors ▸ Entrectinib ▸ Larotrectinib ▸ Repotrectinib • *RET* gene fusion-positive tumors ▸ Pralsetinib ▸ Selpercatinib[d] • Pembrolizumab[g] for TMB-H (≥10 [mut/Mb]) or for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options • Consider if clinical trials or other systemic therapies are not available or appropriate[f]: ▸ Axitinib ▸ Everolimus ▸ Pazopanib ▸ Sunitinib ▸ Vandetanib ▸ Dabrafenib (if *BRAF* positive) (category 2B) ▸ Vemurafenib (if *BRAF* positive) (category 2B)

[a] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.
[b] After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[c] Tyrosine kinase inhibitor (TKI) therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.
[d] Selpercatinib is also FDA approved for pediatric patients 2 years of age or older.
[e] Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.
[f] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[g] See the NCCN Guidelines for Immunotherapy-Related Toxicities for treatment of toxicity from immunotherapy.

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

PRINCIPLES OF SYSTEMIC THERAPY

Medullary carcinoma[a]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Positive for *RET PV* ▸ Selpercatinib (category 1)[d,j]	• Cabozantinib (category 1)[i] • Vandetanib (category 1)[h,i] For symptomatic disease or progression only: • Consider other small-molecule kinase inhibitors[k] • Dacarbazine (DTIC)-based chemotherapy ▸ Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine ▸ Fluorouracil/dacarbazine alternating with fluorouracil/streptozocin	• Positive for *RET PV* ▸ Pralsetinib (category 2B)[j]

[a] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.
[d] Selpercatinib is also FDA approved for pediatric patients 2 years of age and older.
[h] 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.
[i] For symptomatic disease or disease progression, clinical benefit can be seen in both sporadic and FMTC.
[j] Somatic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown
[k] 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.

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

PRINCIPLES OF SYSTEMIC THERAPY[a]

Anaplastic Carcinoma: Neoadjuvant therapy (stage IVa or IVb borderline resectable disease)
• *BRAF* V600E mutation positive ‣ Dabrafenib/trametinib[2] • *RET* gene fusion-positive tumors ‣ Pralsetinib[7] ‣ Selpercatinib[6,d] • *NTRK* gene fusion-positive tumors ‣ Entrectinib[4] ‣ Larotrectinib[6,d] ‣ Repotrectinib

Anaplastic Carcinoma: Adjuvant/Radiosensitizing Chemotherapy Regimens[1]		
Preferred regimen	**Other recommended regimens**	**Useful in certain circumstances**
• None	• Carboplatin/paclitaxel • DocetaxelPaclitaxel	• None

Anaplastic Carcinoma: Systemic Therapy Regimens for Metastatic Disease		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• *BRAF* V600E mutation positive ‣ Dabrafenib/trametinib[2] • *NTRK* gene fusion-positive tumors ‣ Entrectinib[4] ‣ Larotrectinib[3] ‣ Repotrectinib[5] • *RET* gene fusion-positive tumors ‣ Pralsetinib[7] ‣ Selpercatinib[6,d]	• Doxorubicin[8] • Paclitaxel[8] • Carboplatin/paclitaxel[1] (category 2B) • Docetaxel/doxorubicin[1] (category 2B)	• Cisplatin/doxorubicin[8] • Nivolumab[11,12,g,l] • Pembrolizumab[9,g,m] • Pembrolizumab/lenvatinib[10,g] • Pemetrexed/carboplatin if disease progression following prior treatment[23]

[a] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.
[d] Selpercatinib is also FDA approved for pediatric patients 2 years of age and older.
[g] See NCCN Guidelines for Immunotherapy-Related Toxicities for treatment of toxicity from immunotherapy.
[l] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[m] Pembrolizumab is FDA approved for patients with TMB-H [≥10 mut/mb] disease.

References

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

KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA[13-22]

- **Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic MTC and in RAI-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.**

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

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

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 two 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 a patient who is euthyroid 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. Preparation with either thyroid hormone withdrawal or with thyrotropin alfa may be used for treatment of patients with distant metastases. While thyrotropin alfa is not FDA-approved for treatment of distant metastases, a recent meta-analysis reported there was no significant impact on the effectiveness of I-131 therapy for metastatic thyroid cancer depending between either preparation.[2]**
- **Regardless of preparation method, an iodine-restricted diet is recommended for 7 to 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 performed, 24-hour urine collection may document adequate iodine restriction (urine iodine, <50 mcG).[3,4,5] The diet involves a 7 to 14-day reduction in intake of iodized salt, seafood, and dairy products with the intention of optimizing the sensitivity of diagnostic examinations 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 RAI 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 be <48 to 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.**
- **Other organizations have defined RAI-refractory disease as: in the presence of structural disease, no RAI uptake on a diagnostic RAI scan; no RAI uptake present on an RAI scan done several days after RAI therapy; RAI uptake present in some but not other tumor foci; metastatic or disease progression of differentiated thyroid cancer despite RAI uptake; and metastatic or disease progression of differentiated thyroid cancer despite cumulative iodine-131 activity of >22.2 GBq (600 mCi).[6]**

References on THYR-C 5 of 5

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

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.[7,8]
- Adjuvant therapy:
  - 75–150 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)[9]

Special Circumstances

- If treating CNS metastases (including spinal metastases), treatment with high-dose steroid (dexamethasone) is recommended.
- RAI after imaging study or procedure using iodine contrast agent:
  - Wait 2 months to allow for free iodine levels to decrease and allow for optimal RAI uptake.[10,11]
  - Consider measurement of 24-hour urine iodine to confirm a normal free iodine prior to preparing for dosing.
- Breastfeeding patients:
  - Wait 2–6 months after cessation of lactation or with normalization of serum prolactin levels.
  - Complete cessation of breastfeeding after 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.[12]
- 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[13]
  - Multidisciplinary involvement including close monitoring by radiation safety to coordinate administration, monitoring, and minimization of exposure to others
- Pregnancy
  - RAI should be avoided because of risk of fetal hypothyroidism malformation and fetal demise.
  - In selective cases when doses are high or other considerations are present, integrating care with reproductive endocrinology/oncofertility for patients may be appropriate.

References on THYR-C 5 of 5

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

PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
EXTERNAL BEAM RADIATION THERAPY

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 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 (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 ATC, 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 RT 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[14-17]
  - 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

References on THYR-C 5 of 5

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

PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
EXTERNAL BEAM RADIATION THERAPY

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.[18-24] The treating radiation oncologist should use 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[25]
    - ◊ For patients with oligometastatic disease and good performance status, consider higher doses (45–60 Gy) in 1.8–2 Gy daily fractions, or stereotactic body RT 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 (See NCCN Guidelines for Central Nervous System Cancers [BRAIN-C 5 of 8])

Anaplastic Thyroid Cancer

- Adjuvant RT after R0 or R1 resection[17,26-28]
  - Microscopic disease/high-risk regions: 60–66 Gy in 1.2 Gy twice-daily fractions or 1.8–2 Gy daily fractions[27,29]
  - 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[16,17,27]
  - 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[15,16]
  - 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.[16]
- 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
    - ◊ See NCCN Guidelines for Central Nervous System Cancers [BRAIN-C 5 of 8]

References on THYR-C 5 of 5

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

PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF ACTIVE SURVEILLANCE FOR LOW-RISK PAPILLARY THYROID CANCER

Definition of Active Surveillance
- **A treatment plan that involves closely watching a patient's condition but not giving any treatment unless there are changes in test results that show the condition is getting worse.**

Evidence for Active Surveillance
- **There is low quality evidence that active surveillance is an appropriate management option for some patients with low-risk papillary thyroid microcarcinoma (tumor size ≤1 cm[a]), and there are limited data on the role of active surveillance in cancers >1 cm.**

Active Surveillance should not be used in the following scenarios[b]:
- **Patient preference**
- **Tumor characteristics: Aggressive histologic subtypes (if noted on FNA); invasion of recurrent laryngeal nerve, trachea, or esophagus; visible extrathyroidal extension; regional or distant metastases; tumor near posterior capsule; tumors invading the isthmus or abutting against the trachea.**
- **Patient characteristics: Unable or unwilling to follow-up for surveillance.**
- **Physician characteristics: Lack of access to high-quality neck ultrasound.**

Surveillance Strategy
- **Neck ultrasound, with inclusion of thyroid and lymph node regions, should be performed every 6 months for 1 to 2 years and then annually.**

Transitioning to Surgery[c]
- **Patient preference for converting to surgery is an indication, as well as clinical changes, such as new biopsy-proven lymph node metastases; distant metastases; invasion into recurrent laryngeal nerve, trachea, or esophagus; and, radiologic evidence of extrathyroidal extension. In prior studies, cancer growth by 3 mm in any dimension or a 50% volume increase was also an indication for surgical consultation.**

[a] FNA is not recommended in nodules <1 cm with low-risk features.
[b] Determining which patients are candidates for active surveillance involves shared decision making.
[c] Since surgery is the alternative treatment option, surgeons should be involved in discussions on transitioning to surgery.

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

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate for the following:
- Principles of Cancer Risk Assessment and Counseling (EVAL-A)
- Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B)

Papillary and follicular thyroid cancer are features of some inherited cancer syndromes associated with significant clinical implications for the patient and relatives. The most common of these is Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS). PHTS should be suspected if the patient also has a personal or family history of breast cancer, endometrial cancer, colorectal cancer/colorectal hamartomas, multiple mucocutaneous lesions, macrocephaly, and/or a wide range of other features as detailed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. All patients who meet these criteria for PHTS should receive genetic risk assessment, counseling, and testing.

Familial Adenomatous Polyposis (FAP) has been associated with cribriform-morular thyroid cancer. All individuals with cribriform-morular thyroid cancer should receive genetic risk assessment, counseling, and testing for FAP. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal, Endometrial, and Gastric.

Other patients with two or more first-degree relatives who have also had non-medullary thyroid cancer, or who have a personal or family history of multiple other cancers, may be candidates for genetic testing for germline mutations in other hereditary cancer genes.

Hereditary Thyroid Cancer Syndromes
- Cowden Syndrome/PTEN Hamartoma Tumor Syndrome: see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate, COWD-A
- DICER1 syndrome or associated condition (DICER1):
  - Thyroid manifestations: Thyroid neoplasia
  - Other manifestations: Anaplastic sarcoma of the kidney, or Wilms tumor, ciliary body medulloepithelioma (CBME), CNS sarcomas, cystic nephroma, ovarian tumors (Sertoli-Leydig cell tumor, gynandroblastoma, and sarcoma), pleuropulmonary blastoma, pulmonary cysts
  - Surveillance recommendations: see Schultz KAP, Williams GM, Kamihara J, et al. DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies. Clin Cancer Res 2018;24:2251-2261.
- Familial adenomatous polyposis syndrome (APC): see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, FAP-B
- MEN2 (*RET*)
  - Thyroid manifestations: Thyroid cancer (medullary)
  - Other manifestations: Parathyroid adenoma and hyperplasia, pheochromocytomas
  - Surveillance recommendations: MEDU-3

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

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

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

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

Continued

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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 PTC
- Follicular thyroid carcinoma (FTC), NOS
  - FTC, minimally invasive
  - FTC, encapsulated angioinvasive
  - FTC, widely invasive
- **Oncocytic** carcinoma
- Poorly differentiated thyroid carcinoma (used for insular carcinoma as a subtype of poorly differentiated)
- Anaplastic thyroid carcinoma

Continued

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	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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ABBREVIATIONS

ATC	anaplastic thyroid carcinoma
AUS	atypia of undetermined significance
CBC	complete blood count
CBME	competency-based medical education
CEA	carcinoembryonic antigen
CTV	clinical target volume
CNS	central nervous system
CS	Cowden syndrome
dMMR	mismatch repair deficient
DTC	differentiated thyroid cancer
EBRT	external beam radiation therapy
ESRD	end-stage renal disease
ETE	extrathyroidal extension
FAP	familial adenomatous polyposis
FDG	fluorodeoxyglucose
FMTC	familial medullary thyroid carcinoma
FNA	fine-needle aspiration
FTC	follicular thyroid carcinoma
GFR	glomerular filtration rate
GTV	gross tumor volume
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
MEN2A	multiple endocrine neoplasia type 2A
MEN2B	multiple endocrine neoplasia type 2B
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTC	medullary thyroid cancer
NED	no evidence of disease
NIFTP	noninvasive follicular thyroid neoplasm with papillary-like nuclear features
PHTS	PTEN hamartoma tumor syndrome
PTC	papillary thyroid carcinoma
PTV	planning target volume
PV	pathogenic variant
RAI	radioactive iodine
RFA	radiofrequency ablation
SIB	simultaneous integrated boost
SPECT	single-photon emission computed tomography
SRS	stereotactic radiosurgery
TKI	tyrosine kinase inhibitor
Tg ab	antithyroglobulin antibodies
TMB	tumor mutational burden
TSH	thyroid-stimulating hormone
VEGF	vascular endothelial growth factor
WBRT	whole brain radiation therapy

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

Discussion

This discussion corresponds to the NCCN Guidelines for Thyroid Carcinoma. Last updated: August 19, 2024.

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Overview

Epidemiology

Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the U.S. population for individuals ≥50 years 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] Thyroid nodules are approximately four times more common in individuals assigned female at birth (AFAB) than in individuals assigned male at birth (AMAB).

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 44,020 new cases of thyroid carcinoma will be diagnosed in the United States in 2024.[8] As with thyroid nodules, thyroid carcinoma occurs two to three times more often in individuals AFAB than in individuals AMAB. Thyroid carcinoma is currently the eighth most common malignancy diagnosed in individuals AFAB.[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 oncocytic); 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 oncocytic carcinoma, 1.6% had medullary carcinoma, and 0.8% had anaplastic carcinoma.[7] A population-based study of data collected by the International Agency for Research on Cancer from 1998 to 2012 showed that the global incidence of papillary thyroid carcinoma (PTC) increased during this time.[9]

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%.[10,11] In contrast, anaplastic thyroid carcinoma (ATC) 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 oncocytic carcinomas. In 2024, it is estimated that approximately 2170 cancer deaths will occur among persons with thyroid carcinoma in the United States.[8] Though thyroid carcinoma occurs more often in individuals AFAB, mortality rates are lower for younger individuals AFAB.[7,12-14] Although the estimated incidence of thyroid carcinoma previously increased by an average of ~5% annually between 2004 and 2013, the incidence rate has since stabilized, likely due to more conservative indications for thyroid biopsy and the reclassification of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[15] 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).[16-21] However, data show the incidence has increased by varying degrees across all tumor sizes and age groups.[22-31] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[32,33] A cohort study of 2000–2016 data from U.S. cancer registries showed an increase in incidence of aggressive PTC.[34] In addition, an analysis of 1992–2018 SEER data showed that there is no evidence of an improvement in disease-specific survival (DSS) in patients with distantly metastatic differentiated thyroid cancer.[35]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma address management for the different types of thyroid carcinomas including papillary, follicular, oncocytic, medullary, and anaplastic carcinoma. Additional sections in these NCCN Guidelines®

include *Nodule Evaluation, Principles of TSH Suppression, Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma,* and the American Joint Committee on Cancer (AJCC) staging tables.[10] 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.

Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, oncocytic) thyroid carcinoma can be a challenge, because until recently, few prospective randomized trials of treatment have been done.[36,37] 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.[38] The treatment of choice is surgery, followed by radioactive iodine (RAI) ablation (iodine-131) in selected patients and thyroxine therapy in most patients.[11]

Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma.[39] 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.[40] 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 iodine-131.[41] After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary carcinomas after being exposed to iodine-131 fallout.[42] It became evident that iodine-131 and other short-lived iodine-131s were potent thyroid carcinogens in these children, particularly those <10 years when they were exposed.[43] Iodine deficiency increases the risk for radiation-induced thyroid cancer.[44] 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.[45-47] Iodine deficiency is associated with follicular carcinoma and anaplastic carcinomas.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

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 in thyroid cancers published 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.

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; Practice Guidelines; 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 as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, oncocytic) 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.[1,48,49] 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.[50] The other 50% are often first noticed by the patient, usually as an asymptomatic nodule.[1,48]

Fine-needle aspiration (FNA) with ultrasound guidance is the procedure of choice for evaluating suspicious thyroid nodules.[3,49,51] Data show that higher thyroid-stimulating hormone (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.[52-55]

Although >50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present.[56,57] 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.[57,58] Family history of thyroid cancer is also indicative of malignancy. If two or more of these features are present, the likelihood of thyroid cancer is virtually assured; however, this is a rare situation.[58] A patient's age and gender also affect the probability of malignancy. Other factors that increase the suspicion of malignancy include: 1) a history of head and neck irradiation; 2) a history of diseases associated with thyroid carcinoma, such as familial adenomatous polyposis (FAP, formerly called Gardner syndrome), Carney complex, Cowden 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 fluorodeoxyglucose (FDG) uptake on PET or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.[3,59]

For recommendations regarding evaluation of a thyroid nodule that is known or suspected on an exam or from incidental imaging in adults, see guidelines published by the American Thyroid Association (ATA).[3] In 2015, the ATA updated its guidelines on the management of thyroid nodules and thyroid cancer; its comprehensive guidelines also discuss ultrasound and FNA.[3] A statement from the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) committee, which is based on the Breast Imaging Reporting and Data System (BI-RADS) classification for breast cancer, was published in 2017 and also includes recommendations for management of thyroid nodules based on ultrasound findings.[60] Good concordance has been demonstrated between the TI-RADS and Bethesda classification systems.[61] A systematic review including 12 studies with 13,000 patients and 14,867 thyroid nodules showed pooled sensitivity values of 0.89 (95% CI, 0.80–0.95) for the ATA guidelines and 0.84 (95% CI, 0.76–0.89) for ACR TI-RADS for risk stratification of thyroid nodules.[62] Specificity values were much lower: 0.46 (95% CI, 0.29–0.63) for the ATA guidelines and 0.67 (95% CI, 0.56–0.76) for ACR TI-RADS.

FNA and Molecular Diagnostic Results

Cytologic examination of an FNA specimen is typically categorized as: category I: nondiagnostic; category II: benign; category III: atypia of undetermined significance (AUS); category IV: follicular neoplasm or oncocytic neoplasm; category V: suspicious for malignancy; or category VI: malignancy (includes papillary, medullary, anaplastic, or lymphoma). These diagnostic categories for FNA results reflect the 2023 Bethesda System for Reporting Thyroid Cytopathology.[63] The NCCN Guidelines for Thyroid Carcinoma no longer provide management recommendations for nodules classified as Bethesda I and Bethesda II. 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.[64,65] Estimated mean risk of malignancy, inclusive of NIFTP, is 22% (range, 13%–30%) for Bethesda III, 30% (range 23%–34%) for Bethesda IV, 74% (range 67%–83%) for Bethesda V, and 97% (range 97%-100%) for Bethesda VI.[63] If excluding NIFTP, estimated mean risk of malignancy for Bethesda III, IV, V, and VI decrease to 16%, 23%, 65%, and 94%, respectively.[63]

Molecular diagnostic testing to detect individual mutations (eg, *BRAF* V600E, *RET/PTC*, *RAS*, *PAX8/PPAR* 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.[66-76] The *BRAF* V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation.[77] Some studies have linked the *BRAF* V600E mutation to poor prognosis, especially when occurring with *TERT* promoter mutation.[78-81] *BRAF* V600E mutation on its own is generally not considered associated with poor prognosis.[82-84] Indeterminate groups include: 1) follicular or oncocytic neoplasms

(Bethesda IV); and 2) AUS (Bethesda III).[85-87] The NCCN Panel recommends consideration of molecular diagnostic testing for these indeterminate groups.[88,89]

Historically, studies have shown that molecular diagnostics do not perform well for oncocytic carcinoma.[86,90,91] However, modern genomic classifiers have shown promise for diagnosis of oncocytic carcinoma, with sensitivity values ranging from 88.9% to 92.9% and specificity values ranging from 58.8% to 69.3% for detecting oncocytic carcinoma.[92,93] Molecular diagnostic testing may include multigene assays or individual mutational analysis. In addition to their utility in diagnostics, molecular markers are beneficial for making decisions about targeted therapy options for advanced disease and for informing eligibility for some clinical trials. In addition, the presence of some mutations may have prognostic importance.

Follicular lesions are potentially premalignant lesions with a very low, but unknown, malignant potential if not surgically resected. Clinical risk factors, sonographic patterns, and patient preference can help determine whether nodule surveillance or surgery is appropriate for these patients. Guidance regarding nodule surveillance from the ATA and the ACR TI-RADS should be followed, though neither the ATA nor TI-RADS provide nodule surveillance recommendations for nodules with indeterminate cytology.[3,60] A systematic review including 27 studies that evaluated repeat FNA in AUS nodules showed that 48% (95% CI, 43%–54%) of nodules were reclassified as benign, with a negative predictive value (NPV) >96%.[94] FNA may be repeated for AUS, especially if molecular diagnostics are technically inadequate.

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 nodule 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 pretest 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.[95,96] 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.[89,97]

Additional immunohistochemical (IHC) studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of medullary carcinoma.[98] Oncocytic carcinoma 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.[99] Metastatic renal carcinoma can mimic follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma.[98] 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 of the AJCC Staging Manual (see *Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland* on the CAP website).[10,100]

Follicular and oncocytic neoplasms are rarely diagnosed by FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.[38,49,64,101] 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.[102] Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful for follicular neoplasms (see *FNA Results* in the NCCN Guidelines for Thyroid Carcinoma).[56,89,103]

In some patients with follicular lesions, serum TSH level and thyroid iodine-123 or technetium-99m 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.[3,104] 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 *FNA Results* in the NCCN Guidelines for Thyroid Carcinoma).[2,3] Those patients with an increased or normal TSH and with cytology suspicious for follicular or oncocytic neoplasm should undergo diagnostic lobectomy, unless molecular diagnostic testing predicts a low risk of malignancy. In patients with follicular or oncocytic 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 >4 cm (especially in individuals AMAB), invasive cancer, metastatic cancer, or if the patient prefers this approach.

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, 5% to 10% of patients with papillary, follicular, or oncocytic 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, about 75% of patients with differentiated thyroid carcinoma show tumor recurrences during the first 5 years following treatment, with the remaining recurrences occur within 8 years after treatment.[105] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[106,107] In one retrospective multicenter Italian study, including 1020 patients with papillary thyroid cancer who underwent thyroidectomy, recurrences were observed in 1.4%, all of which were located in the cervical lymph nodes or in the thyroid bed.[105] Distant metastases were observed in 3.2%.

It is important to recognize that the poor outcomes in this study were probably related to the manner in which the recurrence was diagnosed. In the past, disease recurrence was heralded by symptoms or palpable disease on physical examination, reflecting relatively large-volume disease recurrence. However, tools that are highly sensitive for detecting disease (eg, sensitive Tg assays, high-resolution neck ultrasound) appear to have resulted in earlier detection of disease recurrence, which is now often found in the first 2 to 5 years of follow-up.[3,108] These nonpalpable, 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.[109,110]

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. Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in individuals AMAB. Prior to the 2017 AJCC 8th edition update,[10] an age cut-off of 45 years was incorporated, based on the 1979 EORTC study.[111]

However, this age cut-off had led to overstaging and, hence, overtreatment. A more up-to-date analysis from an NCCN Member Institution showed that an age cut-off of 55 years predicted the presence of distant metastasis.[112]

The 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. A systematic review including five studies showed that risk of tumor enlargement in patients with PTC undergoing active surveillance was negatively associated with age.[113]

Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good.[114,115] 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.[116] 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.[117-119] 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 treatment.[13,114,120,121] Prognosis is less favorable in individuals AMAB than in individuals AFAB, but the difference is usually small.[13,119] 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 individuals AMAB than in individuals AFAB.[13] Because of this risk factor, individuals AMAB with thyroid carcinoma—especially those who are ≥55 years—may be regarded with special concern.[112]

Familial Syndromes

Familial, non-medullary carcinoma accounts for about 5% of PTCs and, in some cases, may be clinically more aggressive than the sporadic form.[122,123] For patients to be considered as having familial papillary carcinoma, most studies require at least three 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.[124] Other familial syndromes associated with papillary carcinoma are FAP[125] and Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands).[126] The prognosis for patients with all of these syndromes is not different from the prognosis of those with spontaneously occurring papillary carcinoma. For patients with papillary carcinoma, if histology demonstrates cribriform-morular variant, then FAP screening should be done.

Follicular thyroid cancer is a feature of some inherited cancer syndromes associated with significant clinical implications for the patient and relatives. The most common of these is Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS).[127,128] PHTS should be suspected if the patient also has a personal or family history of breast cancer, endometrial cancer, colorectal cancer/colorectal hamartomas, multiple mucocutaneous lesions, macrocephaly, and/or a wide range of other features as detailed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org). All patients who meet these criteria for PHTS should receive genetic risk assessment, counseling, and testing. Other patients with two or more first-degree relatives who have also had non-medullary thyroid cancer, or who have a personal or family history of multiple other cancers, may be candidates for genetic testing for germline mutations in other hereditary cancer genes.

Tumor Variables Affecting Prognosis

Some tumor features have a profound influence on prognosis.[129-132] The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, *BRAF* V600E mutation status, and metastases.[133-135] For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.[136-139] 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).[100] In patients with sporadic medullary carcinoma, a somatic *RET* oncogene mutation confers an adverse prognosis.[140] A meta-analysis including 13 studies showed that programmed death ligand 1 (PD-L1) expression is associated with lower disease-free survival (DFS) (hazard ratio [HR], 3.37; 95% CI, 2.54–4.48; P < .00001) and overall survival (OS) (HR, 2.52; 95% CI, 1.20–5.32; P = .01) in patients with thyroid cancer.[141] Another meta-analysis including 15 studies also showed a significant association between PD-L1 expression and lower DFS (HR, 1.90; 95% CI, 1.33–2.70; P < .001), but OS was not significantly associated with PD-L1 expression.[142] Subgroup analyses showed that the association between PD-L1 expression and DFS was significant for papillary carcinoma (HR, 2.18; 95% CI, 1.08–4.39), but not for poorly differentiated thyroid carcinoma or ATC (HR, 1.63; 95% CI, 0.62–4.32).

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 anaplastic tumor transformation; tall-cell papillary variants, which have a 10-year mortality of ≤25%; columnar variant papillary carcinoma (a rapidly growing tumor with a high mortality rate); hobnail variant papillary carcinoma, which is associated with increased rates of local and distant metastasis; and diffuse sclerosing variants, which infiltrate the entire gland.[38,143-145]

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.[146,147] NIFTP tumors have a low risk for adverse outcomes and, therefore, require less aggressive treatment.[147-151] 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.[146,147] CAP updated its protocols with NIFTP in the June 2017 version.[100] A systematic review including 29 studies showed that the pooled prevalence rates of NIFTP within EFVPTC and PTC were 43.5% (95% CI, 33.5%–54.0%) and 4.4% (95% CI, 2.0%–9.0%), respectively, based on the revised 2016 diagnostic criteria.[152] A 2021 meta-analysis including 50 retrospective studies published between 2016 and 2021 showed that the incidence of NIFTP among PTCs or other thyroid malignancies was 6.0% (95% CI, 4.4%–8.2%).[153]

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 them from papillary subtypes that more frequently show *BRAF* V600E and *RET/PTC* alterations.[70,154-157] 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 one specific molecular test, possibly leading to more aggressive surgical treatment than is necessary.[158,159] Therefore, the validation of molecular diagnostics with NIFTP samples will be necessary to ensure that the tests are accurately classifying these subtypes.

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.[160] 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.[161] FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.[49,101] Therefore, the tumor is often simply referred to as a "follicular neoplasm" by the cytopathologist (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[64] 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.[129] The poor prognosis is closely related to older age at diagnosis, advanced tumor stage, and larger tumor size.[13] 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.[13,162]

When oncocytic cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as oncocytic 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.[10,163] In 2022, the term "Hürthle cell" was replaced with "oncocytic carcinoma."[164] Oncocytic carcinomas tend to be aggressive and associated with poor prognosis.[165,166] However, a retrospective Japanese study (N = 558) has shown that there is not a significant difference in prognosis between oncocytic and follicular thyroid carcinomas.[167]

Oncocytic carcinomas are characterized by somatic mutations in the *RAS/RAF/MAPK* and *PIK/AKT/MTOR* pathways, and in *EIF1AX, TERT*, and *DAXX.* Other unique alterations associated with these cancers include mitochondrial DNA variations and copy number alterations.[168] Benign and malignant oncocytic carcinomas usually cannot be discriminated by FNA or frozen section examination, although large (>4 cm) tumors are more likely to be malignant than smaller ones.[169] Similar to follicular thyroid carcinoma, the diagnosis of oncocytic carcinoma is only assigned after analysis of the permanent histologic sections—obtained from diagnostic lobectomy or thyroidectomy—shows tumor capsule invasion by oncocytic cells.

Primary Tumor Size

PTCs <1 cm, termed "incidentalomas" or "microcarcinomas," are typically found incidentally after surgery for benign thyroid conditions. Their cancer-specific mortality rates are near zero.[170] 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.[171,172] 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,[173] which may be the presenting feature and also may be associated with distant metastases.[170] 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 is 0.4% compared to 7% (P < .001) for tumors ≥1.5 cm.[13] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas.[13]

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.[13,174] Recurrence rates are two times higher with locally invasive tumors, and as many as 33% of patients with such tumors die of cancer within a decade.[13,175]

Lymph Node Metastases

Regional lymph node metastases are most commonly located in the central neck.[3] They are generally associated with worse prognosis in patients with differentiated thyroid cancer, but this association is influenced by other factors such as age. Lymph node metastases are especially associated with worse outcomes in older patients.[176-178] Evidence is less consistent for younger patients. A large retrospective study including 47,902 patients aged <45 years who underwent surgery for stage I PTC showed that cervical lymph node metastases was associated with worse survival outcomes (HR, 1.32; 95% CI, 1.04–1.67; P = .021 for National Cancer Database [NCDB] data; HR, 1.29; 95% CI, 1.08–1.56; P = .006 for SEER data).[179] Another retrospective study showed that, among patients aged <45 years, lymph node involvement was not associated with survival for papillary carcinoma, though increased risk of death was observed for follicular carcinoma.[177] It is important to note that age cut-offs used in these studies were based on previous editions of AJCC staging, as these cut-offs for age at diagnosis for staging increased from 45 to 55 in 2017 (see section above on *Age, Stage, and Sex at Diagnosis*).[10]

Studies examining the association between number of involved lymph nodes and disease outcomes have been inconsistent. One review showed that, among patients with regional node metastasis, number of positive nodes was associated with risk of recurrence.[180] This study emphasized the correlation between the size and number of metastatic lymph nodes and risk of recurrence. Identification of fewer than 5 sub-centimeter 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). Another study of patients aged <45 years showed that number of involved nodes ≤6 nodes was associated with reduced survival.[179] There was no additional mortality risk observed with >6 nodes. Another study showed an association between lymph node ratio (metastatic lymph nodes to total lymph nodes) and disease-specific mortality in patients (N = 10,955) with papillary carcinoma who underwent thyroidectomy with lymph node dissection (HR, 4.33; 95% CI, 1.68—11.18; P < .01).[181]

Distant Metastases

Distant metastases are the principal cause of death from papillary and follicular carcinomas.[182,183] About 50% of these metastases are present at the time of diagnosis.[129] Distant metastases occur even more often in patients with oncocytic carcinoma (35%) and in those patients who are >40 years at diagnosis.[184,185] Among iodine-123 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 age, sites of distant metastases, and whether the metastases concentrate iodine-131.[184-187]

Some pulmonary metastases are compatible with long-term survival.[188] For example, one study found that when distant metastases were confined to the lung, >50% of the patients were alive and free of disease at 10 years, whereas no patients with skeletal metastases survived that long.[189] The survival rates are highest in young patients with diffuse lung metastases seen only on iodine-131 imaging and not on xray.[187,189,190] Prognosis is worse with large pulmonary metastases that do not concentrate iodine-131.[184-186]

Tumor Staging

The NCCN Guidelines for Thyroid Carcinoma do not use TNM (tumor, node, metastasis) 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 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).[10] Many studies (including those described in this Discussion) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[191] and not the 6th, 7th, or 8th editions.[10,192,193] A 2017 study including 1613 patients with resected differentiated thyroid cancer showed that the 8th edition may be superior to the 7th edition for predicting DSS, since fewer patients were categorized as stage III and IV under the 8th edition staging.[194]

Prognostic Scoring Strategies

Several staging and clinical prognostic scoring strategies use patient age >40 years as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma.[117,192,193,195,196] 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.[197] 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.[117]

Unfortunately, a study that classified 269 patients with papillary carcinoma according to five different prognostic paradigms found that some patients in the lowest risk group from each approach died of cancer.[120] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[192,198] 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 <55 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,[199,200] 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.[195,201]

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.[202-205] 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.[206] This allows ongoing reassessment 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

Most NCCN Panel Members recommend total thyroidectomy for patients with biopsy-proven papillary carcinoma under the following circumstances: T3 or larger, clinical N1 disease, M1 disease, aggressive subtype, significant radiation exposure, significant family history, or coexistent thyroid disease. Of all of these clinical features, tumor size is the most debated and is the feature where there is not uniform agreement. Decisions about ipsilateral lobectomy versus total thyroidectomy should be individualized and done in consultation with the patient.[207] A retrospective cohort study including 88 patients with encapsulated well-differentiated thyroid carcinoma >4 cm surgically resected from 1995 to 2021 showed a 10-year DFS and DSS of 100%, respectively.[208] No local, regional, or distant recurrence was observed in this patient sample, including those treated with lobectomy without RAI. Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring[119] and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic Comprehensive Cancer Center for low-risk PTCs (MACIS score ≤3.99) had no improvement in survival rates after undergoing procedures more extensive than ipsilateral lobectomy. Thus, the authors concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[209]

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.[210] No significant differences were found in cancer-specific mortality or distant metastasis rates between the two groups. A 2020 retrospective multicenter study from Spain that evaluated the 2015 ATA recommendation that low-risk papillary carcinoma between 1 cm and 4 cm could receive lobectomy as clinically indicated found that 57.5% of patients who received total thyroidectomy between 2000 and 2017 would have needed thyroidectomy if they had first undergone lobectomy only.[211]

Lobectomy is the recommended treatment for patients with low-risk differentiated thyroid cancer based on 1) the low mortality and low recurrence rates 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.[208,212-216] The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole body iodine-131 imaging. Panel members recommend lobectomy (without RAI ablation) for patients with papillary carcinoma who have incidental small-volume pathologic N1A metastases (<5 involved nodes with no metastasis <2 mm).[217]

NCCN Panel Members believe that 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 ≤1 cm that is unifocal and confined to the thyroid without vascular invasion (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,212,218-220] Lobectomy alone is also adequate treatment for

NIFTP and low-risk pathologies (see *Tumor Variables Affecting Prognosis, Histology*) and minimally invasive follicular thyroid carcinomas (see *Primary Treatment* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

Completion Thyroidectomy

Completion thyroidectomy is recommended when RAI is anticipated or if long-term follow-up is planned with serum Tg determinations and with (or without) whole body iodine-131 imaging. Completion thyroidectomy has a complication rate similar to that of total thyroidectomy. Completion thyroidectomy is recommended for any of the following: positive resection margins, gross extrathyroidal extension, macroscopic multifocal disease (ie, >1 cm), 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.[134,221,222] Blood vessel invasion of <4 vessels does not require completion thyroidectomy in follicular and oncocytic thyroid carcinomas. In patients with local or distant tumor recurrence after lobectomy, cancer is found in >60% of the resected contralateral lobes.[223]

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.[121] 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.[224]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy.[225] Transient clinical hypoparathyroidism postoperatively is common in adults[226] and children[121,227] undergoing total thyroidectomy. One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[228] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[229] Superior laryngeal nerve injury is under-reported and negatively impacts voice projection and high pitch range. 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 four times as many complications.[230]

Radioactive Iodine—Diagnostics and Treatment

Diagnostic Whole Body Imaging and Thyroid Stunning

When indicated, diagnostic whole body iodine-131 imaging is recommended 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 Oncocytic Carcinoma). However, a phenomenon termed "stunning" may occur when imaging doses of iodine-131 induce follicular cell damage.[231] Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent iodine-131.[232] To avoid or reduce the stunning effect, the following have been suggested: 1) the use of small doses of iodine-131 (1–2 mCi) or iodine-123 (2–4 mCi); and/or 2) a shortened interval (<48–72 hours) between the diagnostic iodine-131 dose and the therapeutic dose.[233] Iodine-123 is more expensive, and smaller iodine-131 doses have reduced sensitivity when compared with larger iodine-131 doses.[231,232,234] In addition, a large thyroid remnant may obscure detection of residual disease with iodine-131 imaging. Some experts recommend that diagnostic iodine-131 imaging be avoided completely with decisions based on the combination of tumor stage and serum Tg.[231] Other experts advocate that whole body iodine-131 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.[3,231,235,236] If iodine contrast agent was used with imaging, then RAI should not begin for at least 2 months after the procedure in order to allow for free iodine levels to decrease and thus allow for optimal RAI uptake.[237,238]

Note that diagnostic imaging is used less often for patients at low risk. A false-negative pretreatment scan is possible and should not prevent use of RAI if otherwise indicated (see *Eligibility for Postoperative Radioactive Iodine* in this Discussion, below). For known or suspected distant metastatic disease, diagnostic whole body iodine-123 or iodine-131 imaging before postoperative RAI may be considered.

Eligibility for Postoperative Radioactive Iodine

The NCCN Panel recommends a selective use approach to postoperative RAI administration. The three general, but overlapping, functions of postoperative RAI administration include: 1) remnant ablation, 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 three 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 Oncocytic 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) postoperative unstimulated Tg >10 ng/mL; 3) ≥6 lymph node micrometastases or bulky lymph nodes (based on surgical pathology); 4) significant N1b disease; or 5) differentiated high-grade carcinoma. For papillary carcinoma, vascular invasion is an indication for postoperative RAI. In the case of follicular or oncocytic carcinoma, extensive vascular invasion (≥4 foci) 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 Oncocytic Carcinoma).

Postoperative RAI is selectively recommended for patients who are at greater risk for recurrence with any of the following clinical indications: largest primary tumor >2 cm, high-risk subtypes (for papillary carcinoma), lymphatic invasion, cervical lymph node metastases, macroscopic multifocality (one focus >1 cm), unstimulated postoperative serum Tg (1–10 ng/mL), or microscopic positive margins.[3,239-241] The NCCN Panel does not routinely recommend RAI for patients with all of the following factors: 1) either unifocal (≤2 cm) or multifocal papillary microcarcinomas (classic subtype, all foci ≤1 cm) confined to the thyroid; 2) no detectable anti-Tg antibodies; and 3) postoperative unstimulated Tg <1 ng/mL or stimulated Tg <2 ng/mL. RAI would also not be recommended if a postoperative ultrasound was done (eg, if preoperative imaging was incomplete) and was negative. Minimal extrathyroidal extension alone does not warrant postoperative RAI. 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.[3,242]

Postoperative Administration of RAI

As stated above (see *Eligibility for Postoperative Radioactive Iodine*), use of postoperative RAI administration is dependent on risk for recurrence. Evidence shows that patients with low risk for recurrence do not benefit from adjuvant RAI therapy.[243] However, low-dose RAI (ie, remnant ablation dose) may be used to destroy a thyroid remnant in order to facilitate an undetectable Tg. For patients with intermediate and high risk for recurrence, adjuvant RAI therapy is given with the goal of reducing the risk for recurrence. It is not necessary for there to be suspected disease at time of adjuvant RAI treatment, although it is suspected that recurrence is microscopic disease that progresses later. Finally, RAI therapy may also be used to treat known or suspected structural disease.

Previously, it was reported that postoperative RAI was associated with decreased OS in patients with stage I thyroid cancer, although the deaths seemed unrelated to thyroid cancer.[244] Longer follow-up suggests that OS is not decreased or increased in these patients.[245] However, a 2011 study reported that the incidence of secondary malignancies, such as leukemia and salivary gland malignancies, has increased in patients with low-risk thyroid cancer (ie, T1N0) who received adjuvant RAI.[246] Studies show decreased recurrence and disease-specific mortality for populations at intermediate or higher risk when postoperative iodine-131 therapy is administered as part of the initial treatment.[13,120,247-250] A study of 21,870 patients at intermediate-risk with differentiated thyroid cancer found that postoperative adjuvant 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; $P < .001$).[250]

A phase 3 randomized controlled trial (RCT) including 730 patients with differentiated thyroid cancer that was low risk (defined as multifocal pT1a or pT1b; N0 or Nx; no extrathyroidal extension) showed that receiving no postoperative RAI after thyroidectomy was noninferior to postoperative RAI administration for functional, structural, and biological abnormalities at 3 years.[243] A long-term- study (n = 1298) found that OS is not improved in patients who receive RAI ablation.[251]

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.

Thyroid hormone withdrawal is an option for increasing uptake from RAI treatment. However, two retrospective studies showed that patients with distantly metastatic RAI-avid differentiated thyroid cancer who received recombinant human TSH (rhTSH) in preparation for RAI treatment did not differ significantly in treatment response or survival, compared to patients who received RAI treatment after thyroid hormone withdrawal.[252,253] Duration of time off thyroid hormone depends on the extent of thyroidectomy and approach to hormone replacement in the initial postoperative setting. Guidance for preparing the patient and managing iodine-131 administration can be found in the *Principles of Radiation and Radioactive Iodine Therapy: Iodine-131 Administration* in the NCCN Guidelines for Thyroid Carcinoma.

If RAI ablation is used, the NCCN Guidelines recommend 30 mCi of iodine-131 for RAI ablation in patients at low risk based on randomized trials (category 1).[36,37,254] This same ablation dose—30 mCi—may be considered in patients at slightly higher risk (category 2B).[255] 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.[256] The possible benefits of RAI should be weighed with the risk of adverse effects as part of treatment decision-making.[257] Adverse effects may be minimized by using lower doses of RAI.[36]

Historically, the three methods of determining iodine-131 therapy activities (doses) have included: empiric fixed doses, quantitative dosimetry, and upper bound limits that are set by blood dosimetry.[3,231,258,259] 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 iodine-131 >30 mCi (1110 MBq). However, iodine-131 therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses. Dosimetry can be used to determine the maximal safe dose for treatment of unresectable, large-volume, iodine-concentrating, residual, or recurrent disease.

Administration of a fixed dose of iodine-131 is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of iodine-131 in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of iodine-131. Lymph node metastases may be treated with about 100 to 175 mCi (3700–6475 MBq) of iodine-131. 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 iodine-131, 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 patients who are older and in those with impaired kidney function.[260,261] Diffuse pulmonary metastases that concentrate ≥50% of the diagnostic dose of iodine-131 (which is very uncommon) are treated with ≤150 mCi of iodine-131 (5550 MBq) to avoid lung injury, which may occur when >80 mCi remains in the whole body 48 hours after treatment. Guidance relating to pediatric patients, patients desiring pregnancy, or patients with end-stage renal disease on hemodialysis can be found in the *Principles of Radiation and Radioactive Iodine Therapy: Iodine-131 Administration* in the NCCN Guidelines for Thyroid Carcinoma.

Post-treatment Iodine-131 Imaging

When iodine-131 therapy is given, whole body iodine-131 imaging should be performed several days later to document iodine-131 uptake by the tumor. Post-treatment whole body iodine-131 imaging should be done, primarily because ≤25% of images show lesions that may be clinically important, which were not detected by the diagnostic imaging.[258] In a study of pre-treatment and post-treatment imaging, the two differed in 27% of the treatment cycles, but only 10% of the post-treatment imaging showed clinically significant new foci of metastatic disease.[262] Post-treatment imaging was most likely to reveal clinically important new information in patients <45 years who had received iodine-131 therapy in the past. Conversely, in older patients and patients who had not previously received iodine-131 therapy, post-treatment imaging rarely yielded new information that altered the patient's prognosis.[262] PET scan is indicated for patients with a negative whole body scan who have suspected structural disease based on other imaging methods and/or elevated Tg to a degree that would indicate distant metastasis.[263]

Assessment and Management After Initial Treatment

Serum Tg determinations, neck ultrasound, and whole body iodine-131 imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation.[264] In contrast, neither serum Tg nor whole body iodine-131 imaging is specific for thyroid carcinoma in patients who have not undergone thyroidectomy and remnant ablation.

Measuring Serum Tg and Anti-Tg Antibodies

Evaluation of serum Tg and anti-Tg antibody levels is helpful for the purpose of obtaining a postoperative baseline. Serum Tg measurement is the best means of detecting thyroid tissue, including carcinoma. Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or TSH stimulation. Serum Tg generally does not increase as much after thyrotropin alfa as after withdrawal of thyroid hormone.

Using current Tg assays, patients treated with RAI with measurable serum Tg levels during TSH suppression and those with stimulated Tg levels >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.[265] About 6% of patients who had total thyroidectomy and RAI with detectable serum Tg levels (which are <2 ng/mL but >0.5 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. A 2022 systematic review showed that, among patients who have not had RAI due to low risk of recurrence, Tg levels remain low and stable, indicating that a low cut-off (eg, 1–2.5 ng/mL) may be useful for these patients.[266]

In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for ≤20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.[267] Patients with persistently undetectable serum Tg and anti-Tg antibody levels have longer DFS when compared with patients who have detectable levels.[268]

Functional sensitivity ≤0.1 ng/mL for Tg and ≤0.9 ng/mL for TgAb are reported for newer generation assays, compared to 1.0 ng/mL for Tg and 20 ng/mL for TgAb for older generation assays.[269,270] Tg measurements may also be obtained without stimulating TSH using ultrasensitive assays (ie, second-generation Tg immunometric assays [TgIMAs]).[270,271] With the availability of next-generation assays, it is now widely accepted that stimulated Tg is no longer necessary. 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.[271-273] These antibodies typically falsely lower the Tg value in immunochemiluminometric assays (ICMAs) and immunoradiometric assays (IRMAs), while raising the value in older radioimmunoassays. The conditions for TSH–stimulated, whole body iodine-131 imaging stipulate using 4-mCi iodine-131 doses (based on the trial)[274] and an imaging time of 30 minutes or until 140,000 counts are obtained.

Recombinant Human TSH

During follow-up, periodic withdrawal of thyroid hormone therapy has been used to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements with (or without) iodine-131 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 thyrotropin alfa intramuscularly, which stimulates thyroidal iodine-131 uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.[275] Administration of thyrotropin alfa is well tolerated; nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[274] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[275]

An international study was performed to assess the effects of two rhTSH dosing schedules on whole body iodine-131 imaging and serum Tg levels when compared with imaging and Tg levels obtained after thyroid hormone withdrawal.[274] Data showed that the combination of rhTSH–stimulated whole body imaging and serum Tg measurements detected 100% of metastatic carcinoma.[274] In this study, 0.9 mg of rhTSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of iodine-131 on the third day. Whole body imaging and Tg measurements were performed on the fifth day. Whole body iodine-131 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, obtained 72 hours after the last rhTSH injection, indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole body imaging findings.[274,276]

Treating Patients with Positive Tg and Negative Imaging

Post-treatment iodine-131 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 iodine-131 imaging, neck ultrasonography, CT, MRI, or PET. Pulmonary metastases may be found only after administering therapeutic doses of iodine-131 and obtaining whole body imaging within a few days of treatment.[277] In a study of 283 patients treated with 100 mCi (3700 MBq) of iodine-131, 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.[278]

Unfortunately, most patients who are diagnostic imaging–negative and Tg positive are not rendered disease free by iodine-131 therapy; however, the tumor burden may be diminished.[279] Thus, most patients with residual or recurrent disease confined to the neck undergo reoperation 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 iodine-131 is very low; thus, the tumor will not respond to iodine-131 therapy.

Thyroid Hormone Suppression of TSH

The use of postoperative levothyroxine to decrease TSH levels is considered optimal in treatment of patients with higher-risk papillary, follicular, or oncocytic carcinoma, because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium.[280-283] 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 <0.1 mU/L. For patients who are disease free and at low risk for recurrence, TSH levels should be maintained at the normal range. For patients at low risk of recurrence with imaging negative but Tg levels concerning for disease, TSH levels should be maintained at 0.1–0.5 mU/L. The risks and benefits 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 patients who are older), bone demineralization (particularly in post-menopausal patients), and frank symptoms of thyrotoxicosis.[3,284,285] An adequate daily intake of elemental calcium (1200 mg/day) and vitamin D (1000 units/day) 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.[286,287]

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated with thyroid hormone suppressive therapy.[13,244,248,283,288-290] 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.[244] 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

Evidence regarding use of adjuvant external-beam radiation therapy (EBRT) have largely come from retrospective studies.[291-293] One retrospective study reported a benefit of adjuvant EBRT after RAI in patients >40 years with invasive papillary carcinoma (T4) and lymph node involvement (N1).[294] 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.[247] Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of papillary carcinoma. Similarly, patients with microscopic residual papillary carcinoma postoperatively are more commonly rendered disease free after receiving EBRT (90%) than those who do not receive it (26%).[295] A third study showed that postoperative EBRT was associated with reduced risk of locoregional failure in thyroid cancer that is pT3-4, pN+, or with R1 or R2 resection (N = 254; HR, 0.17; 95% CI, 0.10–0.29; $P < .001$), although no impact was observed on OS ($P = .600$).[296] Another retrospective study suggested that postoperative EBRT may improve survival in patients with macroscopic extrathyroidal extension following surgery.[297] Finally, 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.[298] Other data from single institutions also show that adjuvant EBRT yields long-term control of locoregional disease.[299-301]

Studies suggest that intensity-modulated radiation therapy (IMRT) is safe, effective, and less morbid in patients with thyroid cancer.[296,299,302] A prospective nonrandomized phase 2 study in which 27 patients with gross residual or unresectable thyroid cancer received IMRT with or without concurrent doxorubicin showed locoregional progression-free survival (PFS) and OS rates of 79.7% and 77.3%, respectively.[303] A post hoc analysis showed that use of concurrent doxorubicin was associated with significantly less locoregional failure at 2 years.

There is little evidence regarding appropriate treatment volumes for use of radiation therapy (RT) for thyroid carcinoma, but 60 to 66 Gy for the postoperative setting (≤70 Gy for incomplete resection) is supported by a 2011 review of studies in this area.[293] Additional guidance on EBRT dose and fractionation in the adjuvant setting can be found in the *Principles of Radiation and Radioactive Iodine Therapy: External Beam Radiation Therapy* in the NCCN Guidelines for Thyroid Carcinoma.

External Beam RT and Surgical Excision of Metastases

Surgical excision, EBRT, stereotactic body RT (SBRT), or other local therapies can be considered for symptomatic isolated skeletal metastases or those that are asymptomatic in weight-bearing sites.[304,305] Brain metastases pose a special problem, because iodine-131 therapy may induce cerebral edema. Neurosurgical resection can be considered for brain metastases. For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery (SRS) is preferred over whole brain radiation.[306,307] 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.[308] Most recurrent tumors respond well to surgery, iodine-131 therapy, or RT.[3,309] Local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA) may be considered for select patients with limited burden nodal disease.[3,310]

Systemic Therapy

Systemic therapy can be considered for tumors that are not surgically resectable; are not responsive to iodine-131; are not amenable to RT or other local therapies; and have clinically significant structural disease progression during the last 6 to 12 months. Enrollment in neoadjuvant clinical trials should be encouraged. Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease.[311] Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.[312-319] Agents include multitargeted kinase inhibitors, such as lenvatinib,[312,315,320-327] sorafenib,[328-335] sunitinib,[333,336,337] axitinib,[338-340] everolimus,[341,342] vandetanib,[343] cabozantinib,[313,344] and pazopanib[345]; *BRAF* V600E mutant inhibitors, such as dabrafenib/trametinib[346]; TRK inhibitors, such as larotrectinib, entrectinib, and repotrectinib[347-349]; *RET* inhibitors such as selpercatinib or pralsetinib[350,351]; and anti-programmed cell death protein 1 (PD-1) antibodies such as pembrolizumab.[352,353] Data suggest that ALK inhibitors may be effective in patients with papillary carcinoma who have *ALK* gene fusion.[354-357]

Clinical trials suggest that kinase inhibitors have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of patients, usually for about 12 to 24 months.[315,323,333,345,358-360] Lenvatinib is the preferred systemic therapy option 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 preferred systemic therapy options for the treatment of medullary carcinoma in patients with unresectable locally advanced or metastatic disease, and *RET* inhibitors (selpercatinib and pralsetinib) are preferred options for *RET* mutation-positive disease (see *Medullary Thyroid Carcinoma* in this Discussion and the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Cabozantinib is also an option for RAI-refractory differentiated thyroid carcinoma that has progressed on VEGFR-targeted therapies such as lenvatinib and sorafenib.[361] 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.[322,323,362-367] Dose modifications of kinase inhibitors may be required. Pazopanib has been reported to cause reversible hypopigmentation.[368]

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 and lateral compartments, is the recommended principal imaging modality.[369] 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.[370] Surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients.[371] In more than 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects.[372] Preoperative ultrasound findings altered the operation in >40% of cases. In another report,[373] 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 is a useful adjunct to FNA biopsy in these cases, particularly if cytology is negative. Cross-sectional imaging (CT or MRI) should be performed when suspicious nodes in the neck are detected by ultrasound and/or for vocal cord paresis. Iodinated contrast is required for optimal cervical imaging with CT, although iodinated contrast will delay treatment with RAI; delaying RAI treatment is not harmful. Assessment of vocal cord mobility is recommended for patients with abnormal voice, a surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Evaluation is essential in patients with voice changes. Vocal cord mobility may be evaluated by ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy.[374]

The NCCN Panel agreed on the characteristics of patients at higher risk who require total thyroidectomy as the primary treatment (see *Preoperative or Intraoperative Decision-Making Criteria* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,375,376] A total thyroidectomy is recommended for patients with any one of the following factors, including: known distant metastases, extrathyroidal extension, lateral cervical lymph node metastases or gross central neck lymph node metastases, or poorly differentiated and differentiated high-grade histology. Total thyroidectomy may be considered for patients with bilateral nodularity, tumor >4 cm in diameter, 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. Based on the results of three RCTs, the Panel does not recommend prophylactic central neck dissection if the central compartment lymph nodes are clinically negative. Two trials of patients with cN0 PTC randomized to receive either total thyroidectomy alone or total thyroidectomy plus central neck dissection showed no difference in outcomes between the two groups.[377,378] A third RCT also did not show a significant difference between study arms for structural recurrence but showed that patients with cN0 PTC who received prophylactic central neck dissection with total thyroidectomy were more likely to be upstaged to pN1a than patients who did not receive prophylactic central neck dissection with total thyroidectomy ($P < .05$).[379] Central neck dissection is 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.

Lobectomy is preferred for patients with lower risk PTC, while total thyroidectomy is a category 2B option (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.[225] 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. Most guidelines (eg, NCCN, ATA[3]) do not recommend active surveillance for patients with PTC. However, for PTC ≤1 cm and no concerning lymph node involvement or risk features (eg, posterior location, abutting the trachea or apparent invasion), surgery may not be warranted, and active surveillance with ultrasound may be sufficient.[380-384]

A study of >5000 patients found that patient survival after partial thyroidectomy was similar to survival after total thyroidectomy for patients at low and high risk.[385] An observational study (SEER database) in >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.[386] 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.[244] A study in 52,173 patients found that total thyroidectomy reduces recurrence rates and improves survival in patients with PTC of ≥1 cm when compared with lobectomy.[387]

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), gross positive resection margins, gross extrathyroidal extension, confirmed contralateral disease, vascular invasion, or confirmed nodal metastases. While a retrospective study using the NCDB has shown that a sizable percentage of patients with differentiated thyroid cancer receive RAI therapy following lobectomy,[388] 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.

PTC with lymphatic invasion, poorly differentiated and differentiated high-grade disease (≤1 cm without other high-risk features), or macroscopic multifocal disease (>1 cm) may warrant a completion thyroidectomy (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma); disease monitoring (category 2B) is another option for these patients. Measurement of Tg and anti-Tg antibodies may be useful for obtaining a postoperative baseline, but data to interpret these antibodies in the setting of an intact thyroid lobe are lacking.[389] 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). Disease monitoring is sufficient for tumors resected with lobectomy with all of the following: negative resection margins, no contralateral lesion, no suspicious lymph node(s), and small (≤4 cm) PTCs. Levothyroxine therapy to reduce serum TSH to normal concentrations can be considered for these patients (see *Principles of TSH Suppression* in the NCCN Guidelines for Thyroid Carcinoma).

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 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) postoperative RAI is typically not indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) adjuvant therapy with RAI may be considered for patients with intermediate- or high-risk disease without gross residual disease, and 3) RAI treatment is often used for patients with postoperative residual disease or inoperable distant metastasis based on whether the persistent tumor is shown to be iodine-131–avid. 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). Even in the absence of thyroid bed uptake, postoperative RAI treatment may be considered.

Redifferentiation therapy to re-establish RAI uptake in patients who become RAI-refractory is a strategy that is under investigation. A prospective non-randomized phase II trial including 24 patients with metastatic *BRAF* V600E-mutated differentiated thyroid cancer showed that dabrafenib/trametinib restored RAI uptake in 95.2% of patients.[390] Partial response was observed in 38%, with stable disease observed in 52% of patients. PFS rates (12- and 24-month) were 82% and 68%, respectively, with median PFS not reached. Redifferentiation therapy is also supported by some retrospective case series and chart reviews.[391-393] However, redifferentiation therapy is not recommended in the NCCN Guidelines at this time, as more RCTs are needed in this area.

Prior to administrating RAI, it is important to rule out significant locoregional disease that would first require surgical resection. All patients should have a physical examination of the neck. In patients in whom persistent neck disease is suspected, either due to physical exam findings or biochemical concerns, dedicated neck imaging should be pursued. This can typically be achieved with ultrasound; however, for concerns about gross residual disease, cross-sectional imaging with CT or MRI with contrast is indicated. Palpable neck disease should be surgically resected before any RAI treatment. A negative pregnancy test is required before the administration of RAI in patients of childbearing potential. The administered activity of RAI therapy should be adjusted for pediatric patients.[394] Dose should also be modified if higher than expected uptake, such as in the event of residual thyroid uptake or distant metastasis.

For patients with unresectable gross residual disease in the neck, EBRT can be considered if disease is threatening vital structures, is viscerally invasive, or is rapidly progressing (see *Postsurgical Evaluation* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,299,300,395-397] Enrollment in a neoadjuvant clinical trial should be considered. Patients with bulky, locoregional, viscerally invasive disease or rapid progression should be referred to a high-volume multidisciplinary institution, including referral to a radiation oncologist. Patients with unresectable gross residual disease who received upfront EBRT and with absent RAI should be monitored, or systemic therapy treatment may be considered.

Surveillance and Maintenance

The recommendations for surveillance and maintenance are described in the algorithm (see *Disease Monitoring* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). About 85% of patients are considered to be low risk after surgery for PTC.[281] Standard follow-up includes neck ultrasound and measurement of TSH, Tg, and Tg ab. Concerning results (ie, rising or new Tg ab or abnormal imaging) should result in escalated follow-up. If abnormal imaging, then biopsy of suspicious areas is recommended. Data indicate the potential for unnecessarily intervening on benign structures as opposed to detecting thyroid cancer in patients with low risk for recurrence, previously normal ultrasound, and biochemically excellent response.[398-400] Therefore, patients considered to be at low risk for recurrence may not require long-term ultrasound follow-up. Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.[3] Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.[3]

In patients who have had total (or near total) thyroidectomy and RAI using iodine-131, 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 total thyroidectomy should be followed with physical examination and measurement of TSH, Tg, and Tg ab. RAI imaging 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 Tg ab, or abnormal ultrasound results. Iodine-avid disease that has been treated with a radioisotope and is no longer evident, has a significant biochemical response, or is dramatically reduced in prominence on follow-up imaging beyond 6 months post-therapy may be considered as having responded to treatment. Favorable response to iodine-131 treatment is also assessed through change in volume of known iodine-concentrated lesions by CT or MRI, as well as by decreasing unstimulated or stimulated Tg levels.[3]

Interpretation of new or rising Tg ab is assay dependent and best performed as a radioimmunoassay and with a consistent assay for interpretation of trends. Tg levels remain low and stable in patients who did not receive postoperative RAI treatment, and risk of recurrence is low in these patients.[266] Disease monitoring for these patients is limited to physical exam, neck ultrasound, and measurement of TSH, Tg, and Tg ab. Additional cross-sectional imaging, PET, or RAI imaging may be considered if rising or new Tg ab.

Non-RAI imaging—such as ultrasound of the central and lateral neck compartments, neck CT, chest CT, or FDG-PET/CT—may be considered if RAI imaging is negative. 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 Guidelines for Papillary [Thyroid] Carcinoma). 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. Iodine whole body scan can be used to guide subsequent use of RAI or other follow-up approach.

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 is recommended if the iodine-131 imaging is positive.[401] Local therapies, such as ethanol ablation or RFA, are also an option if available.[402] RT alone is another option in the absence of iodine-131 uptake for select patients not responsive to other therapies.[300,403] EBRT improves local control in patients with gross residual non-RAI–avid disease following surgery.[293] When recurrent disease is suspected based on progressively rising Tg values (basal or stimulated) and negative imaging studies (including PET scans), RAI therapy can be considered using an empirically determined dose of ≥100 mCi of iodine-131 (see *Recurrent Disease* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). No study has shown a decrease in morbidity or mortality in patients treated with iodine-131 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.[404] 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.[405,406] Active surveillance may be considered for patients with low-volume disease that is stable and distant from critical structures.

Metastatic Disease

RAI therapy may be used to treat metastatic disease that is iodine-avid, or local therapies such as ethanol ablation, cryoablation, or RFA may be used for these patients, if available. 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).[3,407] Patients should continue to receive levothyroxine to suppress TSH levels. If not already done, then somatic testing should be done to identify potentially actionable mutations (eg, *ALK, NTRK*, *BRAF*, and *RET* gene fusions; DNA mismatch repair deficiency [dMMR]; microsatellite instability [MSI]; tumor mutational burden [TMB]).

For skeletal metastases, consider surgical palliation for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are RT or other local therapies.[304,305,408-410] 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.[411-413] Embolization (or other interventional procedures) of metastases can also be considered either prior to resection or as an alternative to resection.[408,414] RAI is not likely to be curative, but improved survival has been observed in these patients.[188,415]

For solitary or limited CNS lesions, either neurosurgical resection or SRS is preferred.[306,307] For multiple CNS lesions, RT can be considered,[293] as well as surgical resection for select cases such as for acute decompression (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). For multiple or extensive CNS lesions, radiotherapy (SRS or whole brain RT) is recommended, with resection in select cases. For dosing schedules for CNS metastases, see the NCCN Guidelines for Central Nervous System Cancers (available at www.NCCN.org).

For clinically progressive or symptomatic disease, systemic therapy should be considered.[11] Recommended systemic therapy options include: 1) lenvatinib (preferred) or sorafenib;[322,328] 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.[416,417] Lenvatinib and sorafenib are category 1 options in this setting based on phase 3 randomized trials.[322,328] 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.[320,322,328] 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.[323,418]

Lenvatinib was compared with placebo in patients with metastatic differentiated thyroid cancer that was refractory to RAI in a phase 3 randomized trial.[322] Patients receiving lenvatinib had a PFS of 18.3 months compared with 3.6 months for those receiving placebo (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 regardless of age (using a cut-off of 65 years). Furthermore, a longer median OS was observed in older patients treated with lenvatinib compared to placebo (HR, 0.27; 95% CI, 0.31–0.91; *P* = .20), although patients >65 years also had higher rates of grade 3 and greater adverse effects from treatment. A retrospective analysis of a phase 3 trial demonstrated that patients receiving lenvatinib with ECOG performance status (PS) 0 at baseline had improved PFS (HR, 0.52; 95% CI, 0.35–0.77; *P* = .001), OS (HR, 0.42; 95% CI, 0.26–0.69; *P* = .0004), and response rate (overall response rate [ORR], 3.51; 95% CI, 2.02–6.10; *P* < .0001) compared with patients with a baseline ECOG PS 1.[419] Any-grade treatment-emergent adverse events (TEAEs) occurred in nearly all patients who received lenvatinib, irrespective of ECOG PS at baseline (ECOG PS 0, TEAEs in 100%; ECOG PS 1, TEAEs in 99%). Taken together, these results suggest that lenvatinib is an appropriate treatment option for patients of any age with RAI-refractory differentiated thyroid cancer.[420]

Another phase 3 randomized trial compared sorafenib with placebo in patients with RAI-refractory metastatic differentiated thyroid cancer.[328] 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.

A phase 3 randomized trial compared cabozantinib to placebo in patients with RAI-refractory differentiated thyroid cancer that progressed during or after treatment with one or two VEGFR TKIs (including lenvatinib and sorafenib).[361] Interim analyses of the intention-to-treat (ITT) population (n = 187) showed that the median PFS was not reached in patients receiving cabozantinib, compared with 1.9 months for those receiving placebo (HR, 0.22; 99% CI, 0.13–0.36; *P* < .0001). Serious treatment-related adverse events occurred in 16% of patients in the cabozantinib arm, compared with 2% in the placebo arm, though no treatment-related deaths occurred. At time of extended follow-up, median PFS continued to favor the cabozantinib arm over the placebo arm (11.0 months vs. 1.9 months, respectively; HR, 0.22; 95% CI, 0.15–0.32; *P* < .0001).[421] ORR was 11.0% for the cabozantinib arm, compared to 0% for the placebo arm (*P* = .0003). Subgroup analyses showed that cabozantinib was associated with improved PFS compared to placebo regardless of histology (ie, papillary, follicular, oncocytic, poorly differentiated) and previous VEGFR TKI treatment used (lenvatinib or sorafenib).[422] Cabozantinib is a category 1 option for patients with disease progression after lenvatinib and/or sorafenib.

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 dabrafenib/trametinib (for *BRAF*-positive disease), larotrectinib, entrectinib, or repotrectinib (for *NTRK* gene fusion-positive disease), selpercatinib or pralsetinib (for *RET* 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,[322,328,363,423,424] and caution should be used in patients with untreated CNS metastases due to the associated bleeding risk.[425] The anti-PD-1 antibody pembrolizumab is also an option for patients with TMB-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) disease[353] and for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory treatment options.[352] Active surveillance is often appropriate for asymptomatic patients with indolent disease and no brain metastasis.[323,363]

Palliative care is recommended as indicated for patients with advanced and progressive disease (see the NCCN Guidelines for Palliative Care, available at www.NCCN.org).

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.[49,426] Unlike PTC, FNA is not specific for follicular thyroid carcinoma and accounts for the main differences in management of the two tumor types.[57,64,101,427] 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 neoplasia on FNA are ultimately diagnosed with follicular thyroid carcinoma when the final pathology is assessed. Follicular neoplasms generally do not spread to the lymph nodes, though could spread to soft tissue within the neck. If cervical lymph node metastases are present, then this may indicate misdiagnosis of follicular variant of PTC or a mixed tumor. Molecular diagnostic testing may be useful to determine the status of follicular lesions or lesions of indeterminate significance (including follicular neoplasms or AUS) as more or less likely to be malignant based on the genetic profile.

Because most patients with follicular neoplasms on FNA actually have benign disease, total thyroidectomy is recommended only if radiographic evidence or interoperative findings of extrathyroidal extension are apparent at the time of surgery, or if the patient opts for total thyroidectomy to avoid a second surgery (ie, completion thyroidectomy) if higher risk cancer is found at pathologic review.[426,428] Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery for follicular neoplasia on FNA. If invasive follicular thyroid carcinoma (widely invasive or encapsulated angioinvasive with four or more vessels) 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).

Minimally invasive cancer is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.[3] Lobectomy is preferred for minimally invasive cancers, as well as NIFTP tumors, followed by surveillance, because minimally invasive follicular carcinomas and NIFTP usually have an excellent prognosis. Minimally invasive follicular carcinoma is associated with low mortality, and the Panel feels that the benefit of completion thyroidectomy for small minimally invasive follicular cancers may not justify the additional morbidity.

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) postoperative RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) adjuvant RAI may be recommended for patients with intermediate and high risk for recurrence with the goal of decreasing recurrence risk, and 3) RAI may be used to treat known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

Iodine-131 pre- and posttreatment imaging (with consideration of dosimetry for distant metastasis) is recommended for suspected or proven iodine-131–avid metastatic foci (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). In patients with known or suspected distant metastatic disease, radioiodine diagnostic imaging (iodine-123 or iodine-131) with adequate TSH stimulation (thyroid withdrawal or thyrotropin alfa) should be considered before iodine-131 therapy is administered, with attention to dosing recommendations (see *Principles of Radiation and Radioactive Iodine Therapy* in the NCCN Guidelines for Thyroid Carcinoma) to avoid the problem of stunning, which may limit treatment effect (see section on *Diagnostic Whole Body Imaging and Thyroid Stunning* in this Discussion). 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).

Oncocytic Thyroid Carcinoma

Compared to other types of differentiated thyroid cancer, oncocytic thyroid carcinoma tends to be found at a later stage and is associated with worse prognosis.[165,166] Similar to follicular thyroid carcinoma, oncocytic thyroid carcinoma cannot be diagnosed on FNA. A cytologic result of oncocytic neoplasm has a differential diagnosis of oncocytic thyroid carcinoma as well as several common benign conditions such as adenomas and Hashimoto's thyroiditis. Historically, studies have shown that molecular diagnostics do not perform well for oncocytic neoplasms.[86,90,91] However, with the advent of newer genomic tests, the validity for oncocytic carcinoma is improving (see *FNA and Molecular Diagnostic Results* in this Discussion, above),[91,92] and molecular diagnostics should be considered for oncocytic carcinoma.

The surgical management of oncocytic carcinoma is almost identical to follicular thyroid carcinoma, except that 1) locoregional nodal metastases are more common, and therefore therapeutic lymph node dissections of the affected compartment are needed for clinically apparent biopsy-proven disease; and 2) oncocytic carcinoma is less likely to concentrate iodine-131, compared to other differentiated thyroid carcinomas.[168] Molecular testing may indicate a benign nodule, thus suggesting that observation without surgical intervention may be appropriate. Postoperative EBRT can be considered for: 1) unresectable primary oncocytic carcinomas that do not concentrate iodine-131 if disease is threatening vital structures; and 2) unresectable locoregional recurrence (see *Postsurgical Evaluation* and *Recurrent Disease* in the NCCN Guidelines for Oncocytic [Thyroid] Carcinoma), similar to the management for follicular thyroid carcinoma.

Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Oncocytic [Thyroid] Carcinoma). The NCCN Guidelines provide algorithms to assist in decision-making about use of RAI in different settings: 1) postoperative RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) adjuvant RAI may be recommended for patients with intermediate and high risk for recurrence with the goal of decreasing recurrence risk; and 3) RAI may be used to treat known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Oncocytic [Thyroid] Carcinoma).

Data to support RAI therapy for unresectable disease with positive iodine-131 imaging for oncocytic carcinoma are limited and inconsistent. Iodine-131 therapy (100–150 mCi) may be considered after thyroidectomy for patients with rising or newly elevated Tg levels who have negative scans (including FDG-PET) (see *Recurrent Disease* in the NCCN Guidelines for Oncocytic [Thyroid] Carcinoma).[429] Pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with adequate TSH stimulation (thyroid withdrawal or thyrotropin alfa) may be considered in patients with known or suspected distantly metastatic disease (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Oncocytic [Thyroid] Carcinoma). Since oncocytic carcinoma tends to be non–iodine-avid, negative scans that were done without single-photon emission CT (SPECT) may not detect distant structural disease.

Therefore, if Tg is high and/or pathology is high risk, FDG-PET is indicated.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid.[430-433] 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.[434,435] Familial MTC is now viewed as a variant of MEN2A.[430,431,436] Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of the disease tend to present at earlier ages.[430,431] The 5-year relative survival for stages I to III is about 93%, whereas 5-year survival for stage IV is about 28%.[193,437] 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.[438] Distant metastases in the lungs or bones cause symptoms in 5% to 10% of patients at initial presentation. Many patients with advanced MTC have diarrhea and flushing, because the tumor can secrete calcitonin and sometimes other hormonally active peptides (ie, adrenocorticotropic hormone [ACTH], calcitonin gene-related peptide [CGRP]). Rarely, Cushing syndrome occurs due to tumor ACTH production. Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms.[439] Patients with unresectable or metastatic disease may have either slowly progressive or rapidly progressive disease. Rapid calcitonin and carcinoembryonic antigen (CEA) doubling times are predictive of more aggressive disease. Certain high-grade pathologic features (eg, tumor necrosis, elevated mitotic count, Ki-67 proliferation index) have been found to be associated with worse patient outcomes.[440]

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.[441-443] 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 have benign thyroid disease.[444,445] The ATA is equivocal about routine calcitonin measurement.[3]

Inherited MTC

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.[432,433,446] The *RET* pathogenic variant (PV) codes for a cell membrane-associated tyrosine kinase receptor whose ligand is glial cell line-derived neurotrophic factor. Mutations associated with MEN2A have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; nearly all patients with MEN2B harbor the *RET* M918T mutation found within the intracellular exon 16.[430,431] 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.

Compared with sporadic disease, the typical age of presentation for MEN2A 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. Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically are diagnosed at an earlier age) is probably similar to those with sporadic disease.[447,448] 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.[448]

For patients with known kindreds with inherited MTC, prospective family screening with testing for *RET* PV can identify disease carriers long before clinical symptoms or signs are noted.[432,433] About 6% of patients with clinically sporadic MTC carry a germline *RET* PV, leading to identification of new kindreds with multiple (previously undiagnosed) affected individuals.[449,450] Germline testing for *RET* PV with genetic counseling by a physician or genetic counselor is recommended for all patients with newly diagnosed MTC or clinically suspected sporadic MTC.[451] However, surgery should not be delayed due to awaiting test results. If a germline *RET* mutation is found, then mutation testing should also be done for family members. MTC can involve difficult ethical decisions for clinicians if parents or guardians refuse screening and/or treatment for children with possible MTC.[452] Principles regarding genetic risk assessment can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org).

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum CEA), screening for hyperparathyroidism, and screening for urinary and/or plasma fractionated metanephrines and catecholamines to rule out pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A). Preoperative thyroid and neck ultrasound (including central and lateral neck compartments) is recommended. Contrast-enhanced CT of neck/chest and liver MRI or 3-phase CT of liver can be considered as clinically indicated for metastatic disease. Distant metastasis is not, however, a contraindication to surgery.[430,431] Liver imaging is rarely needed if calcitonin is <500 pg/mL. Evaluation of vocal cord mobility should be performed for patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.

Before surgery for MTC, it is necessary to diagnose coexisting pheochromocytoma. When present, pheochromocytoma should be resected before the MTC to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org). Pheochromocytoma should be removed using laparoscopic adrenalectomy.[430,431,453]

Staging

As previously mentioned, the NCCN Guidelines for Thyroid Carcinoma do not use TNM staging to guide therapy. Instead, many characteristics of the tumor and patient play important roles in disease management. 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).[10] The 8th edition of the AJCC Cancer Staging Manual separated MTC into its own stand-alone chapter.[10] Many of the studies cited in this Discussion reporting on AJCC-TNM staging have referred to the 5th edition of the AJCC-TNM staging[191] and not to the 6th, 7th, or 8th editions.[10,192,193] However, the TNM staging classification lacks other important prognostic factors.[454] Notably absent is the age at diagnosis. Patients <40 years at diagnosis have 5- and 10-year DSS rates of about 95% and 75%, respectively, compared with 65% and 50% for those >40 years.[438,454]

Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor[455]; 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level[456]; and 3) postoperative residual hypercalcitoninemia.[457] 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.[111,454] Codon analysis is useful for predicting prognosis.[430,431,458] Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN2B, is associated with more aggressive disease.[459] 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).[460]

Surgical Management

Surgery is the main treatment for MTC. MTC cells do not concentrate iodine. Therefore, there is no role for iodine-131 in MTC. 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.[430,431] Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease. Testing for a germline *RET* PV is indicated for all patients with MTC.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is ≥1 cm or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is <1 cm and for unilateral thyroid disease (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[375,438]

If a patient with MEN2A is diagnosed early enough, the recommendation is to perform a prophylactic total thyroidectomy, especially in patients with codon 609, 611, 618, 620, 630, or 634 *RET* PV.[430,431,461] Appropriate age of thyroidectomy in children is an evolving field. If the mutation is identified during childhood, then thyroidectomy may be considered. Note that C634 mutations are the most common mutations.[430,431] Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN2B who have codon 883 *RET* PV, 918 *RET* PV, or compound heterozygous (V804M + E805K, V804M + Y806C, or V804M + S904C) *RET* PV (see *Clinical Presentation* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma), because these *RET* PVs carry the highest risk for MTC (ie, level D).[430,431,462]

However, for patients with codon 768, 790, 791, 804, and 891 *RET* (risk level A) PVs, the lethality of MTC may be lower than with other *RET* PVs.[430,431,462,463] In patients with these less high-risk (ie, lower-risk level A) *RET* PVs and no structural evidence of disease, 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).[430,431,464,465] Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.[430,431,463,464,466] A study found no evidence of persistent or recurrent MTC ≥5 years after prophylactic total thyroidectomy in young patients with *RET* PVs for MEN2A; longer follow-up is necessary to determine if these patients are cured.[467]

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.[430,431] 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.

With a concurrent diagnosis of hyperparathyroidism in MEN2A, 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* PV (eg, exons 10, 11, 13–16), which will determine whether they need additional surgery (eg, completion thyroidectomy and/or neck dissection) (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

Adjuvant RT

EBRT has not been adequately studied as adjuvant therapy in MTC.[301,430,468] Slight improvements in local DFS have been reported after EBRT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement.[469] However, most centers do not have extensive experience with adjuvant EBRT for this disease. While therapeutic EBRT may be considered for grossly incomplete resection when additional attempts at surgical resection have been ruled out, adjuvant EBRT is rarely recommended (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[430,431] EBRT can also be given to palliate painful or progressing bone metastases.[304,305,410,430,431] There is little evidence regarding appropriate treatment volumes for use of RT for MTC, but IMRT technique is encouraged, and guidance regarding EBRT dose and fractionation is provided in the *Principles of Radiation and Radioactive Iodine Therapy: External Beam Radiation Therapy* in the NCCN Guidelines for Thyroid Carcinoma.

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 >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.[470] Two studies have reported higher mortality rates for patients with high postoperative serum calcitonin values, with >50% of patients having a recurrence during a mean follow-up of 10 years.[457,471] Routine lymphadenectomy or excision of palpable tumor generally do not 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.[472] 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.[473,474] 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.[474]

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 *Management 2–3 Months Postoperative* 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 MEN, annual screening for pheochromocytoma (MEN2B or MEN2A) and hyperparathyroidism (MEN2A) should also be performed. For some low-risk *RET* PVs (eg, codons 768, 790, 804, or 891), less frequent screening may be appropriate.

Patients with calcitonin ≥150 pg/mL should have CT or MRI of the neck, chest, and liver. Bone scan and whole-body MRI should be considered in select patients such as those with elevated calcitonin levels.[430,431] The NCCN Panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but there is insufficient evidence to recommend any particular choice or combination of tests.[430,431]

For patients with asymptomatic disease and detectable markers in whom imaging does not identify foci of disease, the NCCN Panel recommends conservative surveillance with repeat measurement of the serum markers every 6 to 12 months. Additional imaging studies (eg, FDG-PET/CT, Ga-68 DOTATATE, or MRI with contrast of the neck, chest, and abdomen with liver protocol) may be indicated depending on calcitonin/CEA doubling time. For patients who are asymptomatic with abnormal markers and repeated negative imaging, continued disease monitoring 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 progressing indolent disease.[323,475,476] Vandetanib and cabozantinib are oral receptor kinase inhibitors that improve PFS in patients with metastatic MTC.[477-481] *RET*-specific inhibitors that are options for *RET*-mutated MTC include selpercatinib and pralsetinib.[350,351]

Vandetanib is a multitargeted kinase inhibitor; it inhibits *RET*, VEGFR, and EGFR.[481] In a phase III randomized ZETA trial in patients with unresectable, locally advanced, or metastatic MTC (n = 331), vandetanib improved PFS when compared with placebo (HR, 0.46; 95% CI, 0.31–0.69; *P* < .001); OS data are not yet available.[481] A post-hoc subgroup analysis including 184 patients with symptomatic and progressive disease at baseline also showed improved PFS (HR, 0.43; 95% CI, 0.28–0.64; *P* < .001) in patients who received vandetanib, compared to placebo, although time to worsening pain was not significantly different between the two groups (HR, 0.67; 95% CI, 0.43–1.04; *P* = .07).[482] In this subgroup, the ORR was 37% in patients who received vandetanib and 2% in patients who received placebo (*P* < .001). 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.[483] However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity involving prolongation of the QTc interval.[484] The NCCN Panel recommends vandetanib (category 1) as a preferred option 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 improved median PFS when compared with placebo (11.2 vs. 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; *P* < .001).[477] The median OS 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, 0.64–1.12, *P* = .24).[485] 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 these findings.[485,486] In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC.[487] The NCCN Panel also recommends cabozantinib (category 1) as a preferred option 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.

RET mutations account for a significant percentage of MTC cases,[488-490] supporting investigation into the impact of *RET*-specific inhibitors on *RET*-mutated MTC. Efficacy of the *RET*-specific inhibitor selpercatinib for patients with *RET*-mutant MTC was first evaluated in the phase I–II LIBRETTO-001 study (N = 143), which showed ORR and 1-year PFS rates of 69% (95% CI, 55%–81%) and 82% (95% CI, 69%–90%), respectively, for patients previously treated with vandetanib and/or cabozantinib; and 73% (95% CI, 62%–82%) and 92% (95% CI, 82%–97%), respectively, for patients with no previous vandetanib or cabozantinib treatment.[350] In the phase 3 randomized LIBRETTO-531 trial, selpercatinib was compared to cabozantinib or vandetanib for first-line treatment of progressive *RET*-mutant medullary thyroid cancer (N = 291).[491] At 12-month follow-up, median PFS (not reached vs. 16.8 months, respectively; HR, 0.28; 95% CI, 0.16–0.48; *P* <.001), 12-month PFS rates (86.8%, 95% CI, 79.8%–91.6% vs. 65.7%, 95% CI, 51.9%–76.4%), median treatment failure-free survival rates (not reached vs. 13.9 months, respectively; HR, 0.25; 95% CI, 0.15–0.42; *P* <.001), and 12-month treatment failure-free survival rates (86.2%, 95% CI, 79.1%–91.0% vs. 62.1%, 95% CI, 48.9%–72.8%) were all significantly greater for the selpercatinib arm compared to the control arm. ORRs were 69.4% (95% CI, 62.4%–75.8%) for the selpercatinib arm and 38.8% (95% CI, 29.1%–49.2%) for the control arm. Selpercatinib was also evaluated for the pediatric and adolescent population in the multicenter phase I–II LIBRETTO-121 trial, which included 14 patients with *RET*-mutant medullary thyroid cancer.[492] The ORR for these patients was 83.3%, and the safety profile was comparable to that for adults. Study results are currently only available in abstract form.

Pralsetinib, another *RET*-specific inhibitor, was evaluated in the phase I–II ARROW study, which included 92 patients with *RET*-mutant MTC.[493] The ORR was 60% (95% CI, 46%–74%) in patients previously treated with vandetanib and/or cabozantinib (n = 61) and 74% (95% CI, 49%–91%) in patients with no previous vandetanib or cabozantinib treatment (n = 22). Pralsetinib was generally well-tolerated, with the most commonly reported grade 3–4 treatment-related adverse events being hypertension (11%) and neutropenia (10%). These results are currently reported in abstract form, and the ARROW study is ongoing and continuing to enroll patients.

In 2020, the FDA approved both of these *RET* inhibitors for *RET*-mutated MTC requiring systemic therapy. However, the indication of advanced or metastatic *RET*-mutated MTC for pralsetinib was voluntarily withdrawn by the manufacturer in 2023 due to feasibility of performing confirmatory trials. In 2024, the FDA expanded the approval for selpercatinib to include pediatric and adolescent patients ≥2 years of age. Based on the available data, the NCCN Panel recommends both selpercatinib and pralsetinib as preferred options for patients with *RET*-mutant disease, with selpercatinib being a category 1 option and pralsetinib being a category 2B option (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). *RET* somatic testing should be done in patients who are germline wild-type or if germline status is unknown.

When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended. For unresectable locoregional disease that is symptomatic or progressing by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[494] the following options can be considered: 1) EBRT; or 2) systemic therapy. Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include palliative resection, ablation (eg, radiofrequency, embolization) or other regional treatment, and systemic therapy (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 disease monitoring is acceptable given the lack of data regarding alteration in outcome. If systemic therapy is indicated, then vandetanib and cabozantinib are category 1 preferred options. Selpercatinib (category 1) or pralsetinib (category 2B) are preferred options for patients with *RET*-mutation positive disease. Pembrolizumab is also an option for patients with TMB-H (≥10 mut/Mb) disease, based on results of the phase II KEYNOTE-158 trial, which included two patients with thyroid cancer.[495] TMB is rarely high in MTC. Pembrolizumab is also recommended for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory treatment options, based on the KEYNOTE-158 trial.[352] The NCCN Panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone in the absence of radiographically evident structural disease.

In the setting of symptomatic disease or progression, the NCCN Panel recommends systemic therapy or enrollment in a clinical trial. As stated above for locoregional disease, preferred systemic therapy options include vandetanib (category 1), cabozantinib (category 1), and selpercatinib (category 1) or pralsetinib (category 2B) for patients with *RET*-mutation positive disease. Other small-molecule kinase inhibitors (ie, sorafenib, sunitinib, lenvatinib, pazopanib) may be considered if clinical trials or the NCCN-preferred systemic therapy options are not available or are not appropriate.[336,496-501] If the patient progresses on a preferred option, then systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.[430,502-504] Pembrolizumab is also an option for patients with TMB-H (≥10 mut/Mb) disease and for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory treatment options (useful in certain circumstances).[352,495] EBRT can be used for local symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.[411-413] Best supportive care is also recommended.

Results from clinical trials have shown the effectiveness of novel multitargeted therapies including sunitinib,[336,337] sorafenib,[423,497] lenvatinib,[500] and pazopanib[499] in MTC. Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.[363,366,416,424] Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.[363]

Novel therapies and the management of aggressive MTC have been reviewed.[317,430,505-508] 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.[509] A phase 2 trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with iodine-131.[510] OS was improved in the subset of patients with increased calcitonin doubling times.[511]

Anaplastic Thyroid Carcinoma

ATCs are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[512] Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[513] Fewer than 10% of patients are <50 years, and 60% to 70% of patients are AFAB.[513,514] The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.[512,515] 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.[32]

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.[516] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas undifferentiated carcinomas typically do not. Therefore, iodine-131 imaging and therapy cannot be used.

Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner syndrome, stroke, and hoarseness due to vocal cord paralysis.[517] Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[518,519] The lungs and pleura are the most common sites 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 appearance of ATCs varies widely; many ATCs have mixed morphologies. The most common morphology is biphasic spindle and giant cell tumor. 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 on FNA, and thus, core or surgical biopsy is preferred when the diagnosis of ATC is suspected.[99,520]

Diagnostic procedures include a complete blood count (CBC) with differential, comprehensive metabolic panel, TSH level, direct exam of larynx with evaluation of vocal cord mobility, and imaging studies. Neck ultrasound can rapidly assess tumor extension and invasion.[517] 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.[521] PET/CT or MRI scans 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).[10] Clinically apparent anaplastic tumors are often unresectable. Given the increasing number of therapeutic targets for ATC, tumor testing for actionable mutations (*BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, and TMB) is recommended (see below in the Discussion under *Treatment: Systemic Therapy*).[520] *BRAF* IHC testing is recommended due to faster turnaround compared to genetic testing.

Prognosis

No curative therapy exists for ATC; it is almost uniformly fatal.[522,523] The median survival from diagnosis is about 5 months.[515,524] The 1-year survival rate is about 20%.[519,524] 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.[525] 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.[526] 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.[527-529] A retrospective cohort study conducted at an NCCN Member Institution, including 479 patients diagnosed with ATC between 2000 and 2019, showed that survival rates for this disease are increasing.[530] Treatment factors associated with increased survival in this sample included use of targeted therapy with or without immunotherapy, and neoadjuvant *BRAF*-targeted therapy followed by surgery.

Treatment

ATC has a very poor prognosis and responds poorly to conventional therapy. RAI treatment is not effective in these patients.[520] The role of palliative and supportive care is paramount and should be initiated early in the disease.[520] 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 associated with reduced quality of life and may not be the option a patient would choose.[525,531]

Surgery

Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.[512] Before resection is attempted, the extent of disease—particularly with disease potentially involving the larynx, trachea, esophagus, pharynx, carotid artery, and other neck structures—should be accurately assessed by an experienced surgeon who is capable of complex neck surgery, 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 of treatment.[525] If the patient appears to have resectable disease (potentially curable with surgery), an attempt at total thyroidectomy with complete gross tumor resection should be made, with resection of all involved local or regional structures and nodes.[520] 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.[524,526,532,533] Patients need to receive levothyroxine if total thyroidectomy is done. Tracheostomy may be considered in patients with stage IVc disease if strongly indicated. Prophylactic tracheostomy should be avoided.

Radiation Therapy

EBRT can increase survival in some patients; EBRT can also improve local control and can be used for palliation (eg, to prevent asphyxiation).[468,512,520,528,534-538] Adjuvant RT, especially when combined with concurrent chemotherapy, is associated with improved survival.[539] Higher RT dose is associated with OS in patients with unresected ATC.[540] For solitary brain lesions, either neurosurgical resection or RT is recommended. Once brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months. For unresected or incompletely resected disease, RT, usually with concurrent chemotherapy, should commence as quickly as possible. For R0 or R1 resection, adjuvant RT, usually with concurrent chemotherapy, should begin as soon as the patient has sufficiently recovered from surgery, ideally 2 to 3 weeks postoperatively. IMRT technique is encouraged. 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. For guidance regarding appropriate treatment volumes for use of RT for ATC, see the *Principles of Radiation and Radioactive Iodine Therapy: External Beam Radiation Therapy* in the NCCN Guidelines for Thyroid Carcinoma.

Systemic Therapy

Systemic therapy recommendations are described in the algorithm (see *Systemic Therapy for Anaplastic Thyroid Carcinoma* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma). When systemic therapy is indicated, targeted therapy options are preferred. Dabrafenib plus trametinib combination is an option for *BRAF* V600E mutation-positive tumors,[541] larotrectinib, entrectinib, or repotrectinib are options for *NTRK* gene fusion-positive tumors,[347-349,542] and selpercatinib or pralsetinib are options for *RET* fusion-positive disease.[350,351] Other recommended regimens include paclitaxel and doxorubicin monotherapies.[520] Doxorubicin combined with cisplatin is an option based on a small randomized trial.[543] Paclitaxel combined with carboplatin and docetaxel combined with doxorubicin are also systemic therapy options for patients with metastatic ATC, but these are category 2B options based on low-quality evidence[520] and less Panel consensus. Systemic therapy options for metastatic ATC that are useful in certain circumstances include pembrolizumab,[495] pembrolizumab combined with lenvatinib,[544] and nivolumab.[545,546]

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.[520]

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.[541] The confirmed ORR was 69% (95% CI, 41%–89%), with seven responses ongoing. An updated analysis including 36 patients showed an ORR of 56% (95% CI, 38.1%–72.1%), including 3 complete responses, and 12-month duration of response was 50%.[547,548] Median PFS and OS were 6.7 months and 14.5 months, respectively.[547,548] Twelve-month OS and PFS rates were 43.2% and 51.7%, respectively.[547,548] The combination was found to be well-tolerated as evaluated in 100 patients across seven rare tumor types; common adverse events included fatigue (38%), pyrexia (37%), and nausea (35%).[541] Based on these data, the FDA approved dabrafenib/trametinib for ATC with *BRAF* V600E mutation in 2018.

Since 2018, three TRK inhibitors have been approved by the FDA for treatment of all patients with *NTRK* gene fusion-positive solid tumors. A pooled analysis of three 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 seven patients with thyroid cancer of which one patient had ATC.[347,549] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment.[347,549] One hundred percent of the thyroid cancers in this study responded to larotrectinib, with one complete response and four partial responses.[549] 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.[347] A pooled analysis from a phase II trial and two phase I trials including 54 patients with *NTRK* gene fusion-positive cancer (9% having thyroid cancer) showed an objective response rate of 57.4% for entrectinib, another TRK inhibitor.[348] Finally, repotrectinib was evaluated in a phase I/II study including 88 patients with NTRK gene fusion-positive advanced solid tumors (48 previously treated with a TRK TKI, and 40 who were TRK TKI-naive).[349] The analysis showed an objective response rate of 58% for those who were TRK TKI-naïve, and 50% in those who were previously treated with a TRK TKI. The Panel recommends *NTRK* therapy options such as larotrectinib, entrectinib, and repotrectinib for patients with *NTRK* gene fusion-positive metastatic ATC.

The phase I–II LIBRETTO-001 study evaluated the efficacy of the *RET* inhibitor selpercatinib in 19 patients with previously treated *RET* fusion-positive thyroid cancer (2 patients with anaplastic disease).[350] The ORR was 79% (95% CI, 54%–94%), and 1-year PFS was 64% (95% CI, 37%–82%). In the ongoing phase I–II ARROW study, pralsetinib, another *RET* inhibitor, is being evaluated in patients with *RET* fusion-positive disease (NCT03037385). In an analysis including 9 patients with *RET* fusion-positive thyroid cancer, the ORR was 89% (95% CI, 52%–100%) with durable responses (100% disease control rate [DCR]).[351] In updated analyses including 22 patients with *RET* fusion-positive thyroid cancer (all papillary except for one patient with anaplastic disease), the ORR was 90.9% (95% CI, 70.8%–98.9%), median DOR was 23.6 months, and median PFS was 25.4 months.[550] In 2020, the FDA approved both of these *RET* inhibitors for RAI-refractory *RET* fusion-positive thyroid cancer requiring systemic therapy. In 2024, the FDA expanded the approval for selpercatinib to include pediatric and adolescent patients ≥2 years of age.

The FDA approved the anti-PD-1 antibody pembrolizumab for treatment of previously treated TMB-H (≥10 mut/Mb) solid tumors in 2020 based on results of the phase II KEYNOTE-158 trial, which included two patients with thyroid cancer.[495] For the whole sample, the ORR was 29% (95% CI, 21%–39%). Grade 3–5 treatment-related adverse events were reported in 15% of the patients. A phase II study evaluated another anti-PD-1 antibody, spartalizumab, in 42 patients with locally advanced or metastatic ATC.[551] The ORR was 19% (95% CI, 8.6%–34.1%), but was higher for patients with PD-L1–positive disease (29%; 95% CI, 13.2%–48.7%) and highest in patients with PD-L1 >50% (35%; 95% CI, 14.2%–61.7%). Based on extrapolation from this trial, patients with metastatic ATC may be treated with other PD-1 inhibitors such as pembrolizumab and nivolumab regardless of TMB or combined positive score (CPS). Pembrolizumab combined with lenvatinib for patients with metastatic ATC is also an option supported by a retrospective study including six patients, in which complete response was observed in 66%, with a median PFS of 16.5 months.[544] All patients with a complete response had increased TMB or PD-L1 tumor proportion score (TPS) >50%.

Treatment with anthracyclines and taxanes is generally not very effective for advanced anaplastic disease, although some patients may show disease response or have stable disease.[520,538] Single-agent doxorubicin is approved by the FDA for ATC. A randomized trial including 84 patients with advanced thyroid cancer (not limited to ATC) showed an 11.6% complete response rate in patients who received doxorubicin combined with cisplatin, compared to a complete response in 0 patients who received single-agent doxorubicin.[543] ORR did not differ significantly between the study arms (26% vs. 17%, respectively). Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease.[552-554] If weekly paclitaxel is used, the ATA Guidelines[520] 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.[554]

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.[337,555-563] 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).[555,564]

Preliminary data suggest that *ALK* inhibitors may be effective in a subset of patients with PTC who have *ALK* gene fusions; however, these *ALK* gene fusions are rarely reported in patients with ATC.[354-357]

Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with a subsequent median survival of 1 year.[565] Distant metastases then become the leading cause of death.[566] 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.[538,567-569] IMRT may be useful to reduce toxicity.[468,520,570-574] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival. Other radiosensitizing agents that may be considered include docetaxel and paclitaxel with or without carboplatin.[552,554,571,575] Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN Panel acknowledges that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported.[576]

Multimodality therapy is recommended in patients with locally resectable disease (see *Treatment* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[520,555,570,577-581] Small 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.[582-584] In a case series, complete surgical resection without tracheostomy or radical re-resection was achieved in six patients with initially unresectable *BRAF* V600E-mutated ATC who received neoadjuvant dabrafenib/trametinib.[585] One-year OS was 83%, and the local control rate (LCR) was 100%. Two patients eventually died from distant metastasis, but the treatment response continued to be durable in the remaining four patients.

Neoadjuvant dabrafenib/trametinib for *BRAF* V600E-mutated ATC may be considered for patients with resectable disease, though this is a category 2B option based on less Panel consensus.[585]

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