NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thyroid Carcinoma

NCCN Evidence Blocks™

Version 3.2023 — July 27, 2023

NCCN Evidence Blocks™

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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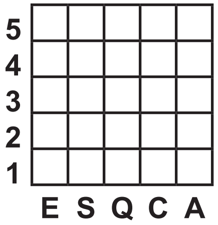
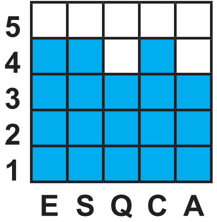
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

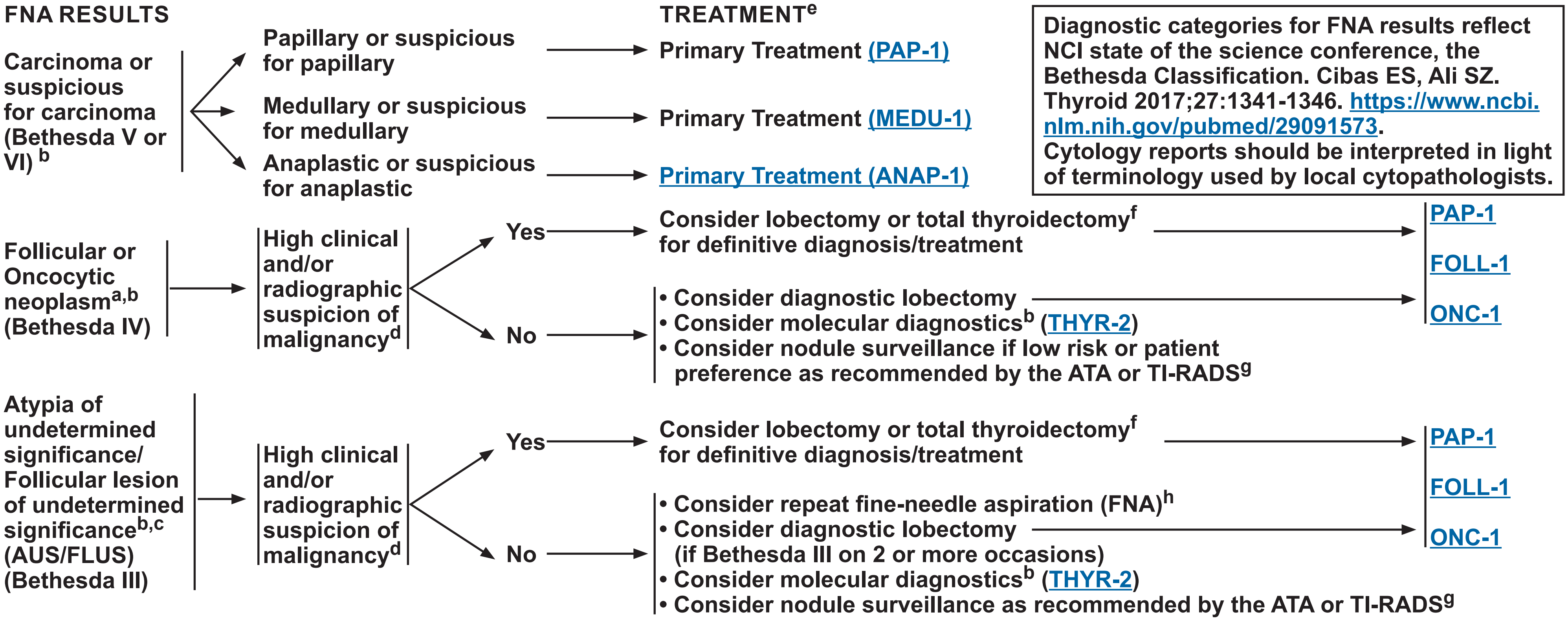
5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**



FNA RESULTS

TREATMENT[e]

Carcinoma or suspicious for carcinoma (Bethesda V or VI) [b]

- **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)**

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

Follicular or Oncocytic neoplasm[a,b] **(Bethesda IV)** → **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 as recommended by the ATA or TI-RADS**[g]

Atypia of undetermined significance/ Follicular lesion of undetermined significance[b,c] **(AUS/FLUS) (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 diagnostic lobectomy (if Bethesda III on 2 or more occasions)** → **PAP-1, FOLL-1, ONC-1**
  - **Consider molecular diagnostics**[b] **(THYR-2)**
  - **Consider nodule surveillance as recommended by the ATA or TI-RADS**[g]

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

[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, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1 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 5% or less), consider nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient. If molecular diagnostics are technically inadequate or not done, then repeat FNA.

[c] Estimated risk of malignancy is 6%–18% exclusive of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (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 oncocytic neoplasm (Bethesda IV), history of radiation exposure, or contralateral lobe lesions.

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

[h] Consider second opinion pathology.

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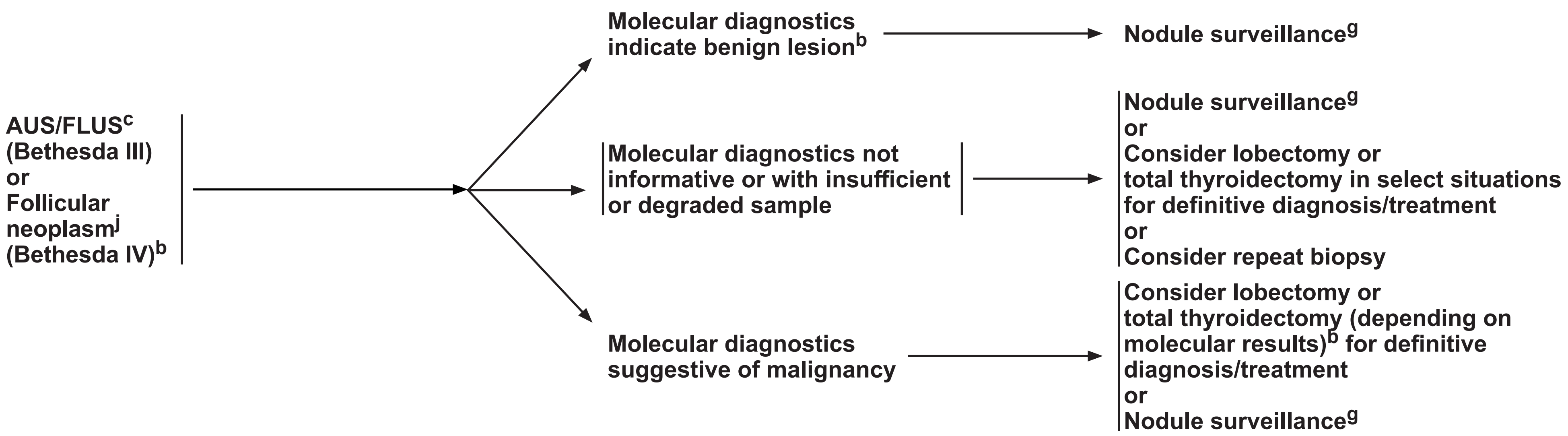
MOLECULAR DIAGNOSTIC RESULTS

TREATMENT[i]



AUS/FLUS[c] (Bethesda III) or Follicular neoplasm[j] (Bethesda IV)[b]

Molecular diagnostics indicate benign lesion[b] → **Nodule surveillance[g]**

Molecular diagnostics not informative or with insufficient or degraded sample →
Nodule surveillance[g]
or
Consider lobectomy or total thyroidectomy 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]

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

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[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, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1 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 5% or less), consider nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient. If molecular diagnostics are technically inadequate or not done, then repeat FNA.

[c] Estimated risk of malignancy is 6%–18% exclusive 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).

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

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

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FNA RESULTS | **DIAGNOSTIC PROCEDURES** | **PREOPERATIVE OR INTRAOPERATIVE DECISION-MAKING CRITERIA** | **PRIMARY TREATMENT**

Papillary carcinoma or suspicious for papillary carcinoma

>1 cm →

- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- CT/MRI with contrast for locally advanced disease 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]

→ Indications for total thyroidectomy (any present):
- Known distant metastases
- Extrathyroidal extension
- Tumor >4 cm in diameter
- Lateral cervical lymph node metastases or gross central neck lymph node metastases
- Poorly differentiated
- Consider for prior radiation exposure (category 2B)
- Consider for bilateral nodularity

→ Total thyroidectomy[g]
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 (preferred) + isthmusectomy (category 2B) → Post-Lobectomy (PAP-2)

≤1 cm → Thyroid and neck ultrasound (including central and lateral compartments), if not previously done

→ No concerning lymph node(s) → Active surveillance[f] with ultrasound or Lobectomy[e] → Post-Lobectomy (PAP-2)

→ Concerning lymph node(s) → Manage as ≥1 cm (see pathway above)

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[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] If otherwise low risk pathology, lobectomy without completion is an appropriate option.

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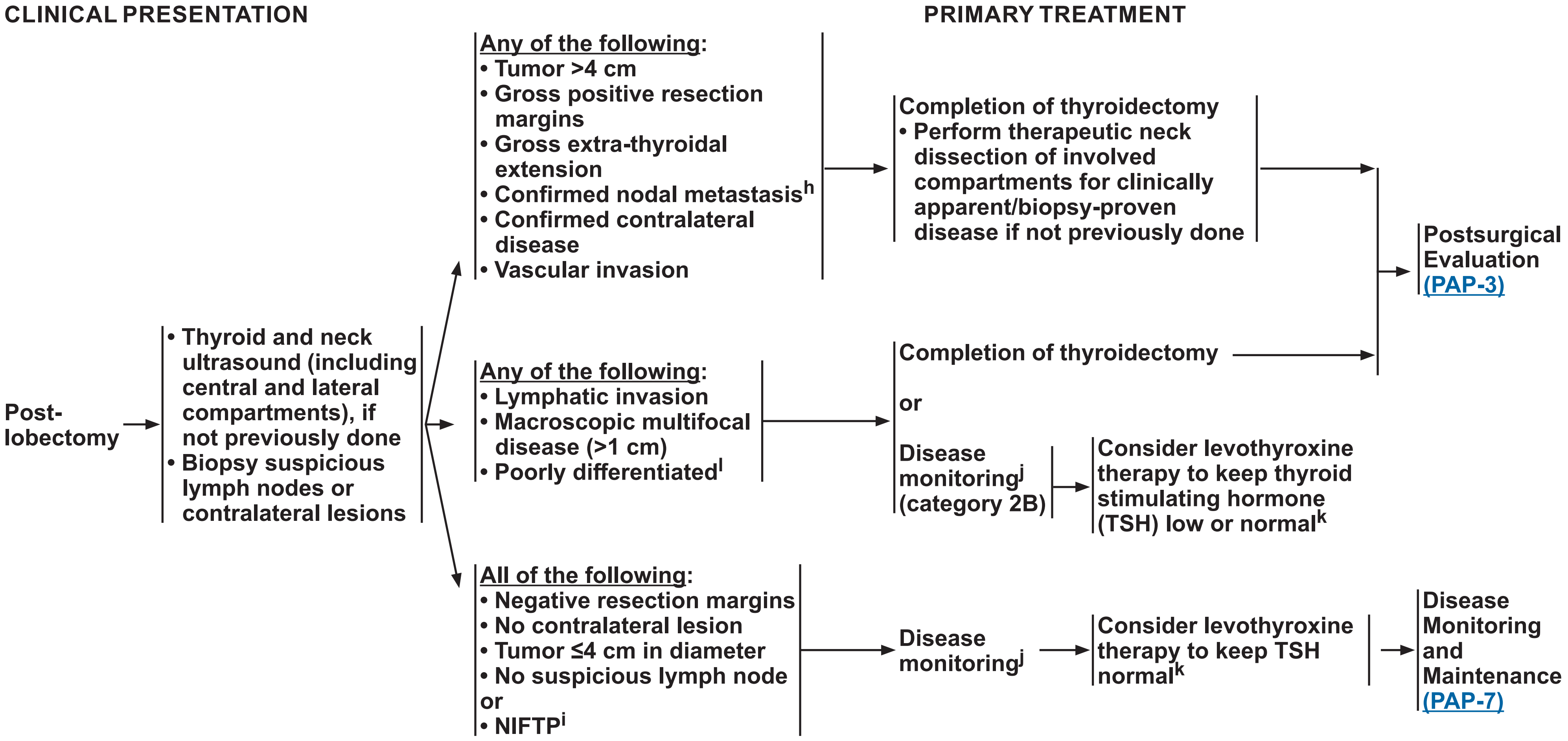

CLINICAL PRESENTATION

PRIMARY TREATMENT

Post-lobectomy →

- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- Biopsy suspicious lymph nodes or contralateral lesions

→ **Any of the following:**
- Tumor >4 cm
- 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:**
- Lymphatic invasion
- Macroscopic multifocal disease (>1 cm)
- Poorly differentiated[l]

→ **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
- Tumor ≤4 cm in diameter
- No suspicious lymph node

or
- NIFTP[i]

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

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[h] Completion of thyroidectomy is not required for incidental small volume pathologic N1A metastases (<5 involved nodes with no metastasis <2 mm) 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] 1 cm or less, without other high-risk features.

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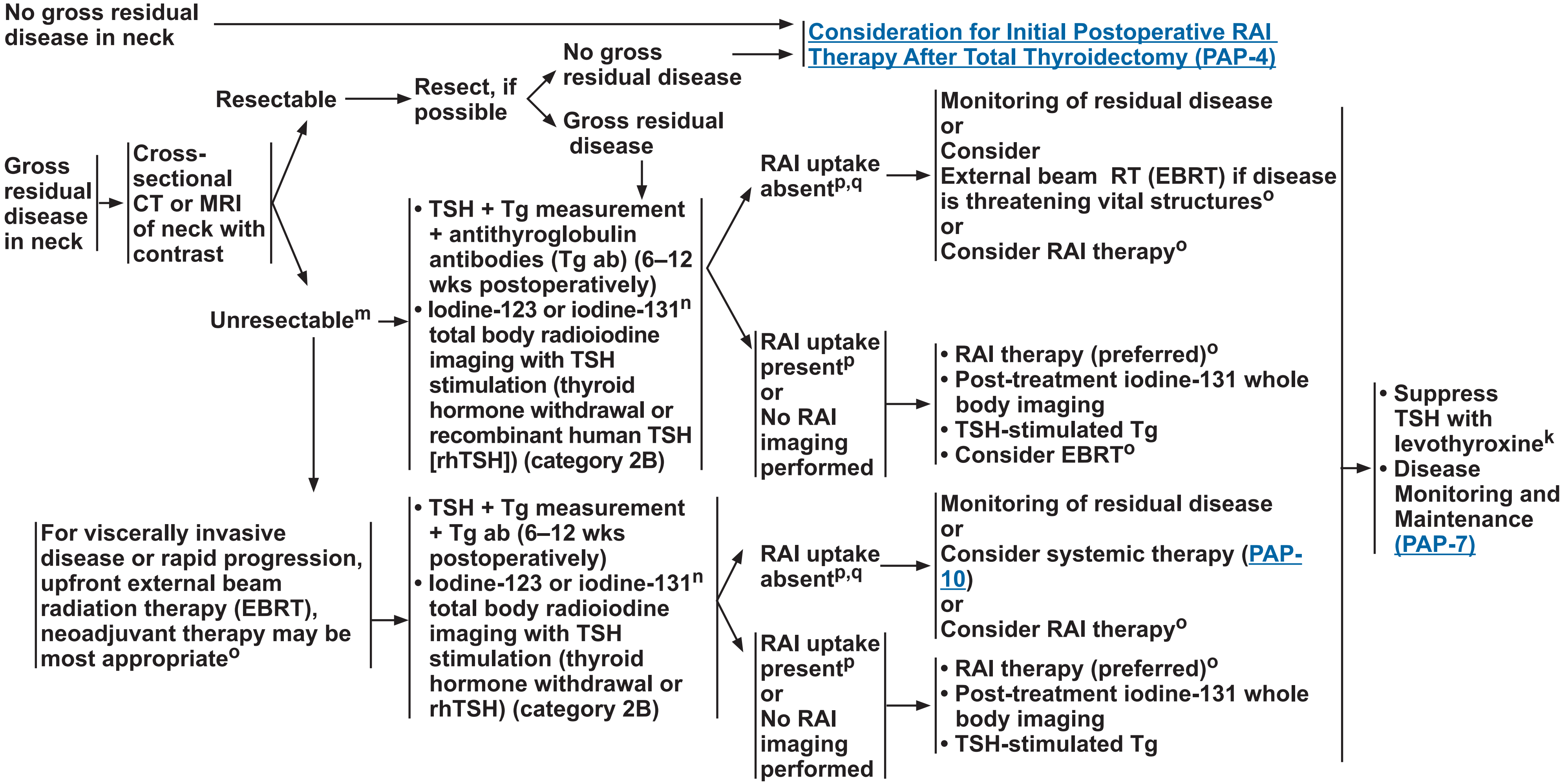
POSTSURGICAL EVALUATION



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 wks postoperatively)**
    - **Iodine-123 or iodine-131[n] total body radioiodine imaging with TSH stimulation (thyroid hormone withdrawal or recombinant human TSH [rhTSH]) (category 2B)**
      - **RAI uptake absent[p,q]** → **Monitoring of residual disease or Consider External beam RT (EBRT) if disease is threatening vital structures[o] or Consider RAI therapy[o]**
      - **RAI uptake present[p] or No RAI imaging performed** →
        - **RAI therapy (preferred)[o]**
        - **Post-treatment iodine-131 whole body imaging**
        - **TSH-stimulated Tg**
        - **Consider EBRT[o]**
- **Unresectable[m]** → (same evaluation as above)
  - **For viscerally invasive disease or rapid progression, upfront external beam radiation therapy (EBRT), neoadjuvant therapy may be most appropriate[o]** →
    - **TSH + Tg measurement + Tg ab (6–12 wks postoperatively)**
    - **Iodine-123 or iodine-131[n] total body radioiodine imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH) (category 2B)**
      - **RAI uptake absent[p,q]** → **Monitoring of residual disease or Consider systemic therapy (PAP-10) or Consider RAI therapy[o]**
      - **RAI uptake present[p] or No RAI imaging performed** →
        - **RAI therapy (preferred)[o]**
        - **Post-treatment iodine-131 whole body imaging**
        - **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).

[m] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.

[n] If considering dosimetry, iodine-131 is the preferred agent.

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

[p] If higher than expected uptake (residual thyroid uptake or distant metastasis), change dose accordingly.

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

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CLINICOPATHOLOGIC FACTORS

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

→ RAI not typically indicated (PAP-7)

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

→

CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

RAI is not required in patients with classic PTC who have T1b/T2 (1–4 cm) N0 or NX disease or small-volume N1a disease (fewer than 5 metastatic lymph nodes with <2 mm of focus of cancer in node), particularly if the postoperative Tg is <1 ng/mL in the absence of interfering 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[u]
- Primary tumor >4 cm
- Postoperative unstimulated Tg >10 ng/mL[r,v]
- Bulky or >5 positive lymph nodes
- Vascular invasion

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

Known or suspected distant metastases at presentation (PAP-6)

Gross residual disease not amenable to RAI therapy (PAP-10)

---

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

[s] If preoperative imaging incomplete, postoperative imaging should evaluate central and lateral neck.

[t] eg, poorly differentiated, tall cell, columnar cell, hobnail variants, diffuse sclerosing, insular.

[u] Minimal extrathyroidal extension alone likely does not warrant RAI.

[v] 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.

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

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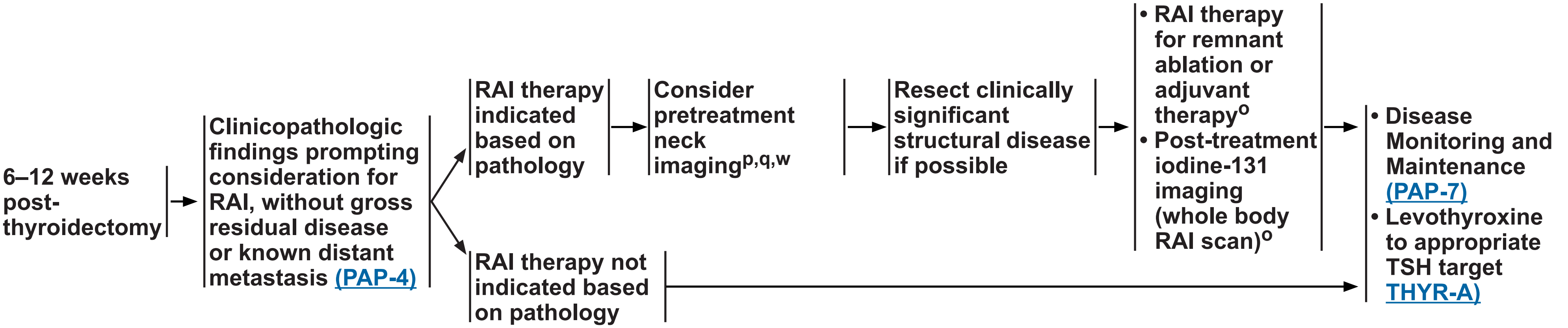
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



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**[p,q,w] → **Resect clinically significant structural disease if possible** →
- **RAI therapy for remnant ablation or adjuvant therapy**[o]
- **Post-treatment iodine-131 imaging (whole body RAI scan)**[o]

→
- **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)**

---

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

[p] If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

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

[w] 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.

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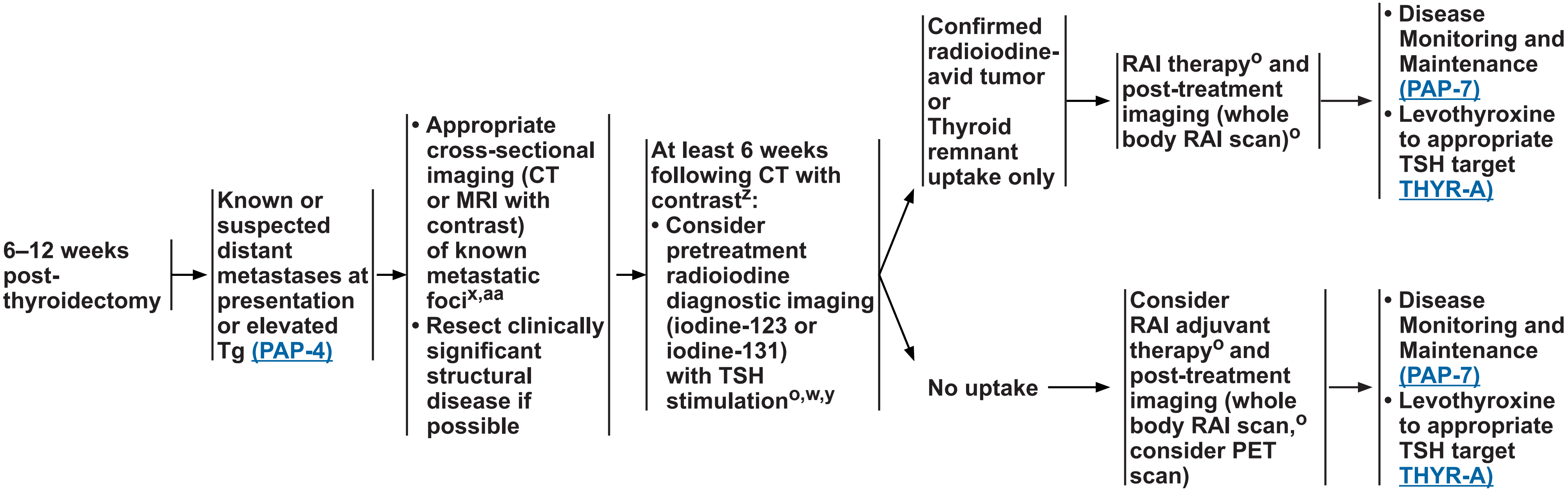
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



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[x,aa]
- Resect clinically significant structural disease if possible

→ At least 6 weeks following CT with contrast[z]:
- Consider pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with TSH stimulation[o,w,y]

Confirmed radioiodine-avid tumor or Thyroid remnant uptake only → RAI therapy[o] and post-treatment imaging (whole body RAI scan)[o] →
- Disease Monitoring and Maintenance (PAP-7)
- Levothyroxine to appropriate TSH target THYR-A)

No uptake → Consider RAI adjuvant therapy[o] and post-treatment imaging (whole body RAI scan,[o] consider PET scan) →
- Disease Monitoring and Maintenance (PAP-7)
- Levothyroxine to appropriate TSH target THYR-A)

---

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

[w] 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.

[x] 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.

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

[z] Consider 24-hour urine iodine.

[aa] If suspicion of pulmonary metastasis, chest CT can be done without contrast.

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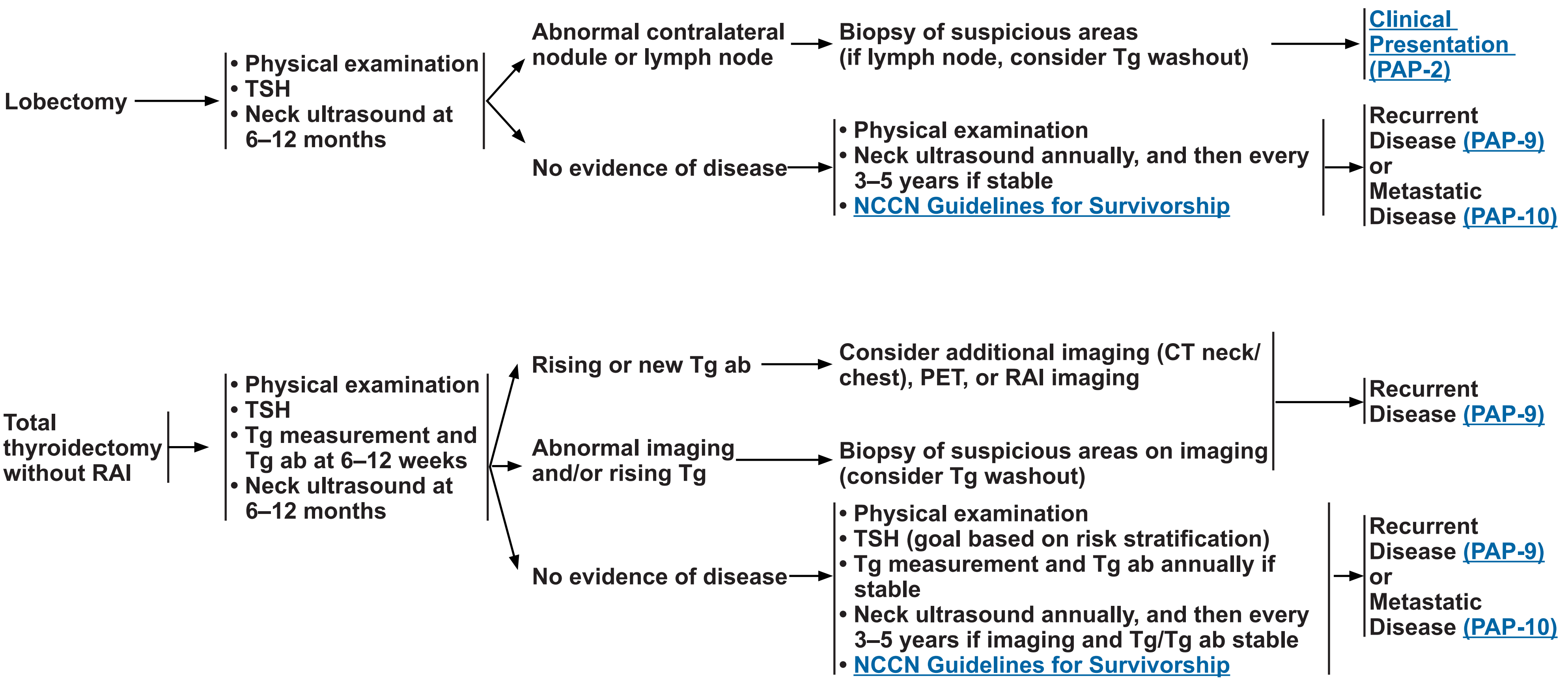

TREATMENT | **DISEASE MONITORING** | **FINDINGS** | **MANAGEMENT**

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 annually, and then every 3–5 years if stable
- 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 annually, and then every 3–5 years if imaging and Tg/Tg ab stable
- NCCN Guidelines for Survivorship

→ **Recurrent Disease (PAP-9) or Metastatic Disease (PAP-10)**

Total thyroidectomy with RAI (PAP-8)

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TREATMENT | **DISEASE MONITORING** | **FINDINGS** | **MANAGEMENT**

Total thyroidectomy with RAI

- **RAI-avid disease present on post-therapy scan** →
  - **Disease monitoring:**
    - Physical examination
    - Neck ultrasound at 6–12 months
    - TSH
    - Tg measurement and Tg ab[bb]
    - Consider TSH-stimulated RAI whole body scan
  - **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** →
    - Consider biopsy of suspicious areas on imaging with Tg washoutFollow-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
    - NCCN Guidelines for Survivorship

    → Recurrent Disease (PAP-9) or Metastatic Disease (PAP-10)

- **RAI-avid disease absent on post-therapy scan** →
  - **Disease monitoring:**
    - Physical examination
    - Neck ultrasound at 6–12 months
    - TSH
    - Tg measurement and Tg ab[bb]
  - **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** → Consider biopsy of suspicious areas on imaging with Tg washout → Recurrent Disease (PAP-9)
  - **No evidence of disease** →
    - Physical examination
    - TSH[k]
    - Tg measurement and Tg ab yearly if stable
    - Neck ultrasound annually for 5 years, and then less often if imaging and Tg measurement and Tg ab stable
    - NCCN Guidelines for Survivorship

    → Recurrent Disease (PAP-9) or Metastatic Disease (PAP-10)

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

[bb] 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.

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RECURRENT DISEASE

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

Suppress TSH with levothyroxine[k]

Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (PAP-7)

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

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

Locoregional recurrence

Consider iodine total body scan

Surgery (preferred) if resectable[ee]
and
Consider radioiodine treatment,[dd] if 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[o]**
  and/or
- **Systemic therapies (Treatment of Metastatic Disease 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[o]
and/or
Local therapies when available[ff]
and/or
If not amenable to RAI (Treatment of Metastatic Disease PAP-10)

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

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

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

- **Continue to suppress TSH with levothyroxine[k]**
- **For advanced, progressive, or threatening disease, genomic 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)**
- **Consider clinical trial**

→ **Unresectable locoregional recurrent/ persistent disease**

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

→ **Bone metastases [(PAP-11)](#)**

→ **CNS metastases [(PAP-12)](#)**

Unresectable locoregional recurrent/persistent disease; Soft tissue metastases →

- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **◊ Lenvatinib (category 1)[gg]**
  - **Other Recommended Regimens**
    - **◊ Sorafenib (category 1)[gg]**
  - **Useful in Certain Circumstances**
    - **◊ Cabozantinib (category 1) if progression after lenvatinib and/or sorafenib**
    - **◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - **◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - **◊ Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
    - **◊ Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - **◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[hh,ii]**
- **Consider resection of distant metastases and/or RT[o] or other local therapies[ff] when available to metastatic lesions if progressive and/or symptomatic [(Locoregional disease PAP-9)](#)**
- **Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[gg] [(PAP-7)](#)**
- **Best supportive care, [NCCN Guidelines for Palliative Care](#)**

[See Evidence Blocks on PAP-10A](#)

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[k] [Principles of TSH Suppression (THYR-A)](#).

[o] [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. [Principles of Kinase Inhibitor Therapy (THYR-B)](#).

[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

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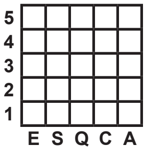

EVIDENCE BLOCKS FOR IODINE-REFRACTORY RECURRENT, PERSISTENT, OR METASTATIC PAPILLARY THYROID CARCINOMA

Preferred Regimen	
Lenvatinib	
Other Recommended Regimen	
Sorafenib	
Useful in Certain Circumstances	
Cabozantinib (if progression after lenvatinib and/or sorafenib)	
Larotrectinib (for *NTRK* gene fusion-positive tumors)	
Entrectinib (for *NTRK* gene fusion-positive tumors)	
Pralsetinib (for *RET*-fusion positive tumors)	
Selpercatinib (for *RET*-fusion positive tumors)	
Pembrolizumab (for TMB-H tumors)	
Pembrolizumab (MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)	
Dabrafenib/trametinib (for *BRAF* V600E mutation)	

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

Bone metastases →

- **Consider surgical palliation and/or RT[o]/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[kk]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[gg] (PAP-7)**
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **Lenvatinib (category 1)[gg]**
  - **Other Recommended Regimens**
    - **Sorafenib (category 1)[gg]**
  - **Useful in Certain Circumstances**
    - **Cabozantinib (category 1) if progression after lenvatinib and/or sorafenib**
    - **Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - **Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
    - **Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - **Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[gg,hh,ii]**
- **Best supportive care, NCCN Guidelines for Palliative Care**

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[o] 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. Principles of Kinase Inhibitor Therapy (THYR-B).

[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

[jj] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

[kk] 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.

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

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery (SRS)[o] is preferred or**
- **For multiple CNS lesions, consider radiotherapy, including whole brain radiotherapy RT (WBRT) or SRS,[o] and/or resection in select cases**
  and/or
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - ◊ **Lenvatinib (category 1)[gg,ll,mm]**
  - **Other Recommended Regimens**
    - ◊ **Sorafenib (category 1)[gg,ll,mm]**
  - **Useful in Certain Circumstances**
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    - ◊ **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
      and/or
    - ◊ **Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - ◊ **Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[gg,hh,ii,kk]**
- **Best supportive care, NCCN Guidelines for Palliative Care**

---

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

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

[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

[jj] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

[kk] 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.

[ll] After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.

[mm] Tyrosine kinase inhibitor (TKI) therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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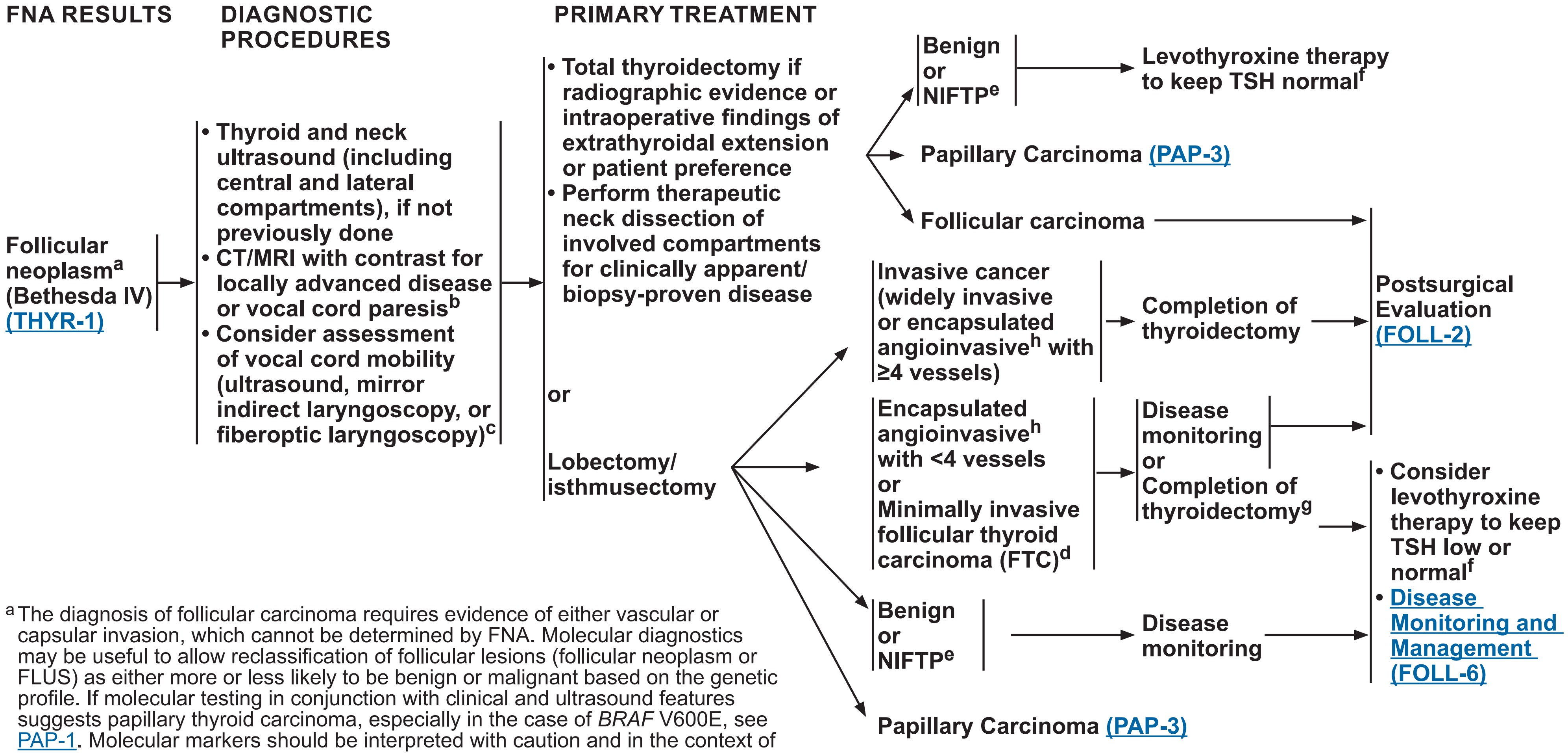

FNA RESULTS

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

DIAGNOSTIC PROCEDURES

- **Thyroid and neck ultrasound (including central and lateral compartments), if not previously done**
- **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]**

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**

or

Lobectomy/ isthmusectomy

Benign or NIFTP[e] → **Levothyroxine therapy to keep TSH normal[f]**

Papillary Carcinoma (PAP-3)

Follicular carcinoma → **Postsurgical Evaluation (FOLL-2)**

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] → **Disease monitoring or Completion of thyroidectomy[g]**

Disease monitoring → **Postsurgical Evaluation (FOLL-2)**

Completion of thyroidectomy[g] →
- **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)

---

[a] The diagnosis of follicular carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (follicular neoplasm or FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing in conjunction with clinical and ultrasound features suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.

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

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

[d] Minimally invasive 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.

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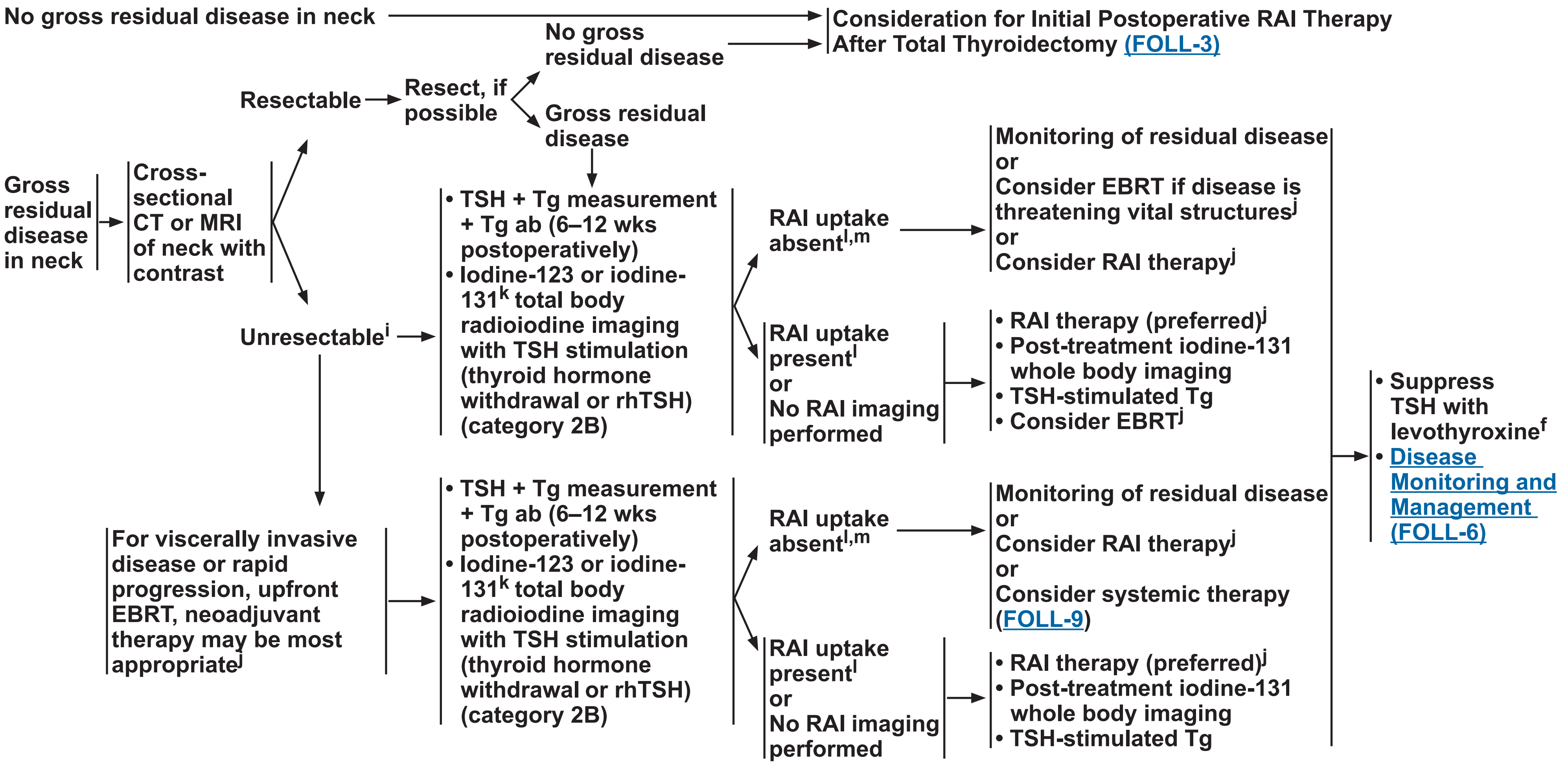
POSTSURGICAL EVALUATION



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** →
    - **TSH + Tg measurement + Tg ab (6–12 wks postoperatively)**
    - **Iodine-123 or iodine-131[k] total body radioiodine imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH) (category 2B)**
      - **RAI uptake absent[l,m]** → **Monitoring of residual disease or Consider EBRT if disease is threatening vital structures[j] or Consider RAI therapy[j]**
      - **RAI uptake present[l] or No RAI imaging performed** →
        - **RAI therapy (preferred)[j]**
        - **Post-treatment iodine-131 whole body imaging**
        - **TSH-stimulated Tg**
        - **Consider EBRT[j]**
- **Unresectable[i]** →
  - **TSH + Tg measurement + Tg ab (6–12 wks postoperatively)**
  - **Iodine-123 or iodine-131[k] total body radioiodine imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH) (category 2B)**
  - (see above for RAI uptake absent / present pathways)
  - **For viscerally invasive disease or rapid progression, upfront EBRT, neoadjuvant therapy may be most appropriate[j]** →
    - **TSH + Tg measurement + Tg ab (6–12 wks postoperatively)**
    - **Iodine-123 or iodine-131[k] total body radioiodine imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH) (category 2B)**
      - **RAI uptake absent[l,m]** → **Monitoring of residual disease or Consider RAI therapy[j] or Consider systemic therapy (FOLL-9)**
      - **RAI uptake present[l] or No RAI imaging performed** →
        - **RAI therapy (preferred)[j]**
        - **Post-treatment iodine-131 whole body imaging**
        - **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).

[i] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.

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

[k] If considering dosimetry iodine-131 is the preferred agent.

[l] If higher than expected uptake (residual thyroid uptake or distant metastasis), change dose accordingly.

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

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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 or stimulated Tg <2 ng/mL[n]
- Negative postoperative ultrasound, if done[o]

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

RAI selectively recommended (if any present):
- Largest primary tumor 2–4 cm
- Minor vascular invasion (<4 foci)
- Cervical lymph node metastases[r]
- Postoperative unstimulated Tg 1–10 ng/mL[n]
- 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):
- Significant N1b disease
- Gross extrathyroidal extension[p]
- Primary tumor >4 cm
- Extensive vascular invasion (≥4 foci)
- Postoperative unstimulated Tg >10 ng/mL[n,q]
- Bulky or >5 positive lymph nodes[r]

→ **RAI Being Considered (FOLL-4)**

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

Gross Residual Disease Not Amenable to RAI Therapy (FOLL-9)

[n] Tg values obtained 6–12 weeks after total thyroidectomy.
[o] If preoperative imaging incomplete, postoperative imaging should evaluate central and lateral neck.
[p] Minimal extrathyroidal extension alone likely does not warrant RAI.
[q] 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.
[r] Consider evaluation for follicular variant of PTC if cervical lymph node involvement is present.

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

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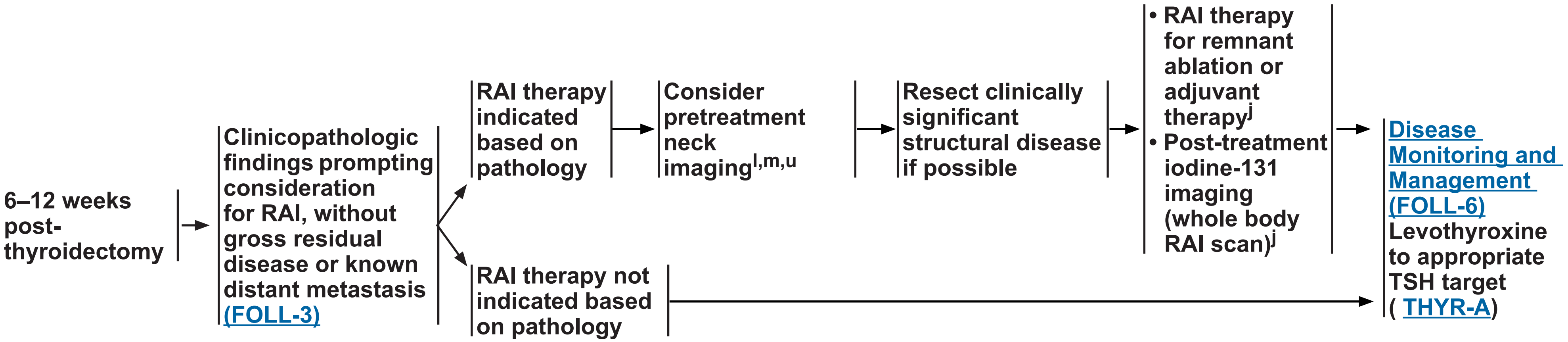
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



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[l,m,u] → Resect clinically significant structural disease if possible →
  - RAI therapy for remnant ablation or adjuvant therapy[j]
  - Post-treatment iodine-131 imaging (whole body RAI scan)[j]

  → 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)

---

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

[l] If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

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

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

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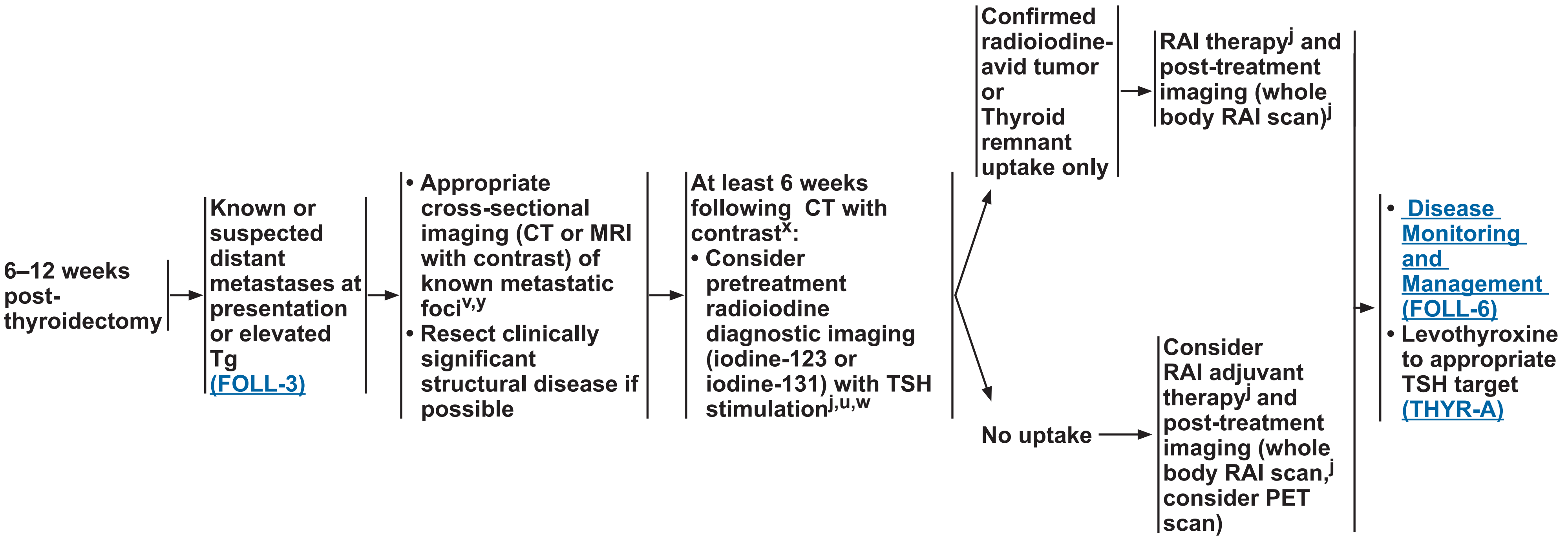
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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[v,y]
- Resect clinically significant structural disease if possible

→

At least 6 weeks following CT with contrast[x]:
- Consider pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with TSH stimulation[j,u,w]

→ Confirmed radioiodine-avid tumor or Thyroid remnant uptake only → RAI therapy[j] and post-treatment imaging (whole body RAI scan)[j]

→ No uptake → Consider RAI adjuvant therapy[j] and post-treatment imaging (whole body RAI scan,[j] consider PET scan)

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

---

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

[u] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative 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.

[v] 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.

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

[x] Consider 24-hour urine iodine.

[y] If suspicion of pulmonary metastasis, chest CT can be done without contrast.

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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 annually, and then every 3–5 years if stable
- 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 annually, and then every 3–5 years if imaging and Tg/Tg ab stable
- NCCN Guidelines for Survivorship

→ Recurrent Disease (FOLL-8) or Metastatic Disease (FOLL-9)

Total thyroidectomy with RAI (FOLL-7)

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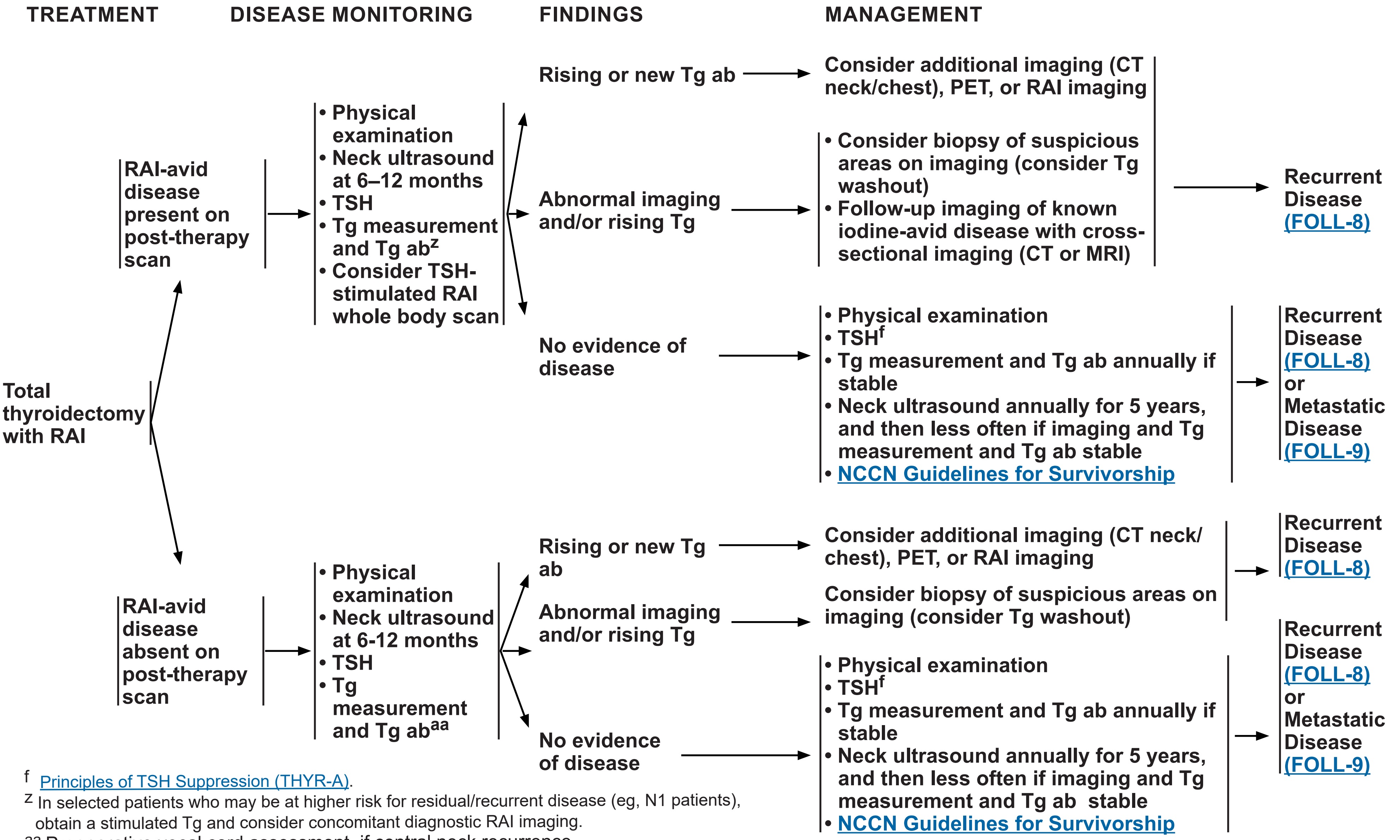

TREATMENT | **DISEASE MONITORING** | **FINDINGS** | **MANAGEMENT**

Total thyroidectomy with RAI

RAI-avid disease present on post-therapy scan →
- Physical examination
- Neck ultrasound at 6–12 months
- TSH
- Tg measurement and Tg ab[z]
- Consider TSH-stimulated RAI whole body scan

Rising or new Tg ab → **Consider additional imaging (CT neck/chest), PET, or RAI imaging**

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**
- **NCCN Guidelines for Survivorship**

→ **Recurrent Disease (FOLL-8) or Metastatic Disease (FOLL-9)**

RAI-avid disease absent on post-therapy scan →
- Physical examination
- Neck ultrasound at 6-12 months
- TSH
- Tg measurement and Tg ab[aa]

Rising or new Tg ab → **Consider additional imaging (CT neck/chest), PET, or RAI imaging**

Abnormal imaging and/or rising Tg → **Consider biopsy of suspicious areas on imaging (consider Tg washout)**

→ **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**
- **NCCN Guidelines for Survivorship**

→ **Recurrent Disease (FOLL-8) or Metastatic Disease (FOLL-9)**

---

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

[z] 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.

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

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RECURRENT DISEASE

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

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

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

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

Locoregional recurrence → **Consider iodine total body scan** →

Surgery (preferred) if resectable[aa]
and
Consider radioiodine treatment,[cc] if 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[j]**
  and/or
- **Systemic therapies (Treatment of Metastatic Disease 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[j]
and/or
Local therapies when available[dd]
and/or
If not amenable to RAI FOLL-9

---

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

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

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

[bb] 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.

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

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

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

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

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

→ **Unresectable locoregional recurrent/ persistent disease**

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

→ **Bone metastases (FOLL-10)**

→ **CNS metastases (FOLL-11)**

Unresectable locoregional recurrent/persistent disease; Soft tissue metastases →

- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **◊ Lenvatinib (category 1)[ee]**
  - **Other Recommended Regimens**
    - **◊ Sorafenib (category 1)[ee]**
  - **Useful in Certain Circumstances**
    - **◊ Cabozantinib if progression after lenvatinib and/or sorafenib**
    - **◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - **◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - **◊ Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
    - **◊ Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - **◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ff,gg]**
- **Consider resection of distant metastases and/or EBRT[j] or other local therapies[dd] when available to metastatic lesions if progressive and/or symptomatic. (Locoregional disease FOLL-8)**
- **Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[gg] (FOLL-6)**
- **Best supportive care, NCCN Guidelines for Palliative Care**

See Evidence Blocks on FOLL-9A

---

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

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

[dd] Ethanol ablation, cryoablation, RFA, etc

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

[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

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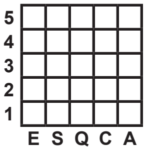

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

EVIDENCE BLOCKS FOR IODINE-REFRACTORY RECURRENT, PERSISTENT, OR METASTATIC FOLLICULAR THYROID CARCINOMA

Preferred Regimen	
Lenvatinib	
Other Recommended Regimen	
Sorafenib	
Useful in Certain Circumstances	
Cabozantinib (if progression after lenvatinib and/or sorafenib)	
Larotrectinib (for *NTRK* gene fusion-positive tumors)	
Entrectinib (for *NTRK* gene fusion-positive tumors)	
Pralsetinib (for *RET*-fusion positive tumors)	
Selpercatinib (for *RET*-fusion positive tumors)	
Pembrolizumab (for TMB-H tumors)	
Pembrolizumab (MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)	
Dabrafenib/trametinib (for *BRAF* V600E mutation)	

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

Bone metastases →

- **Consider surgical palliation and/or RT[j]/other local therapies[dd] when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage**
- **Consider embolization or other interventional procedures as alternatives to surgical resection/RT in select cases[j]**
- **Consider intravenous bisphosphonate or denosumab[ii]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[ee] (FOLL-6)**
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **Lenvatinib (category 1)[ee]**
  - **Other Recommended Regimens**
    - **Sorafenib (category 1)[ee]**
  - **Useful in Certain Circumstances**
    - **Cabozantinib if progression after lenvatinib and/or sorafenib**
    - **Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - **Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
    - **Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - **Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ee,ff,gg]**
- **Best supportive care, NCCN Guidelines for Palliative Care**

---

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

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

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

[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

[hh] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

[ii] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.

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

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or SRS is preferred**
  or
- **For multiple CNS lesions, consider radiotherapy,[j] including WBRT or SRS,[j] and/or resection in select cases**
  and/or
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - ◊ **Lenvatinib (category 1)[ee,jj,kk]**
  - **Other Recommended Regimens**
    - ◊ **Sorafenib (category 1)[ee,jj,kk]**
  - **Useful in Certain Circumstances**
    - ◊ **Cabozantinib if progression after lenvatinib and/or sorafenib**
    - ◊ **Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - ◊ **Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - ◊ **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
      and/or
    - ◊ **Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - ◊ **Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ee,ff,gg,ii]**
- **Best supportive care, NCCN Guidelines for Palliative Care**

---

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

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

[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

[hh] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

[ii] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.

[jj] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.

[kk] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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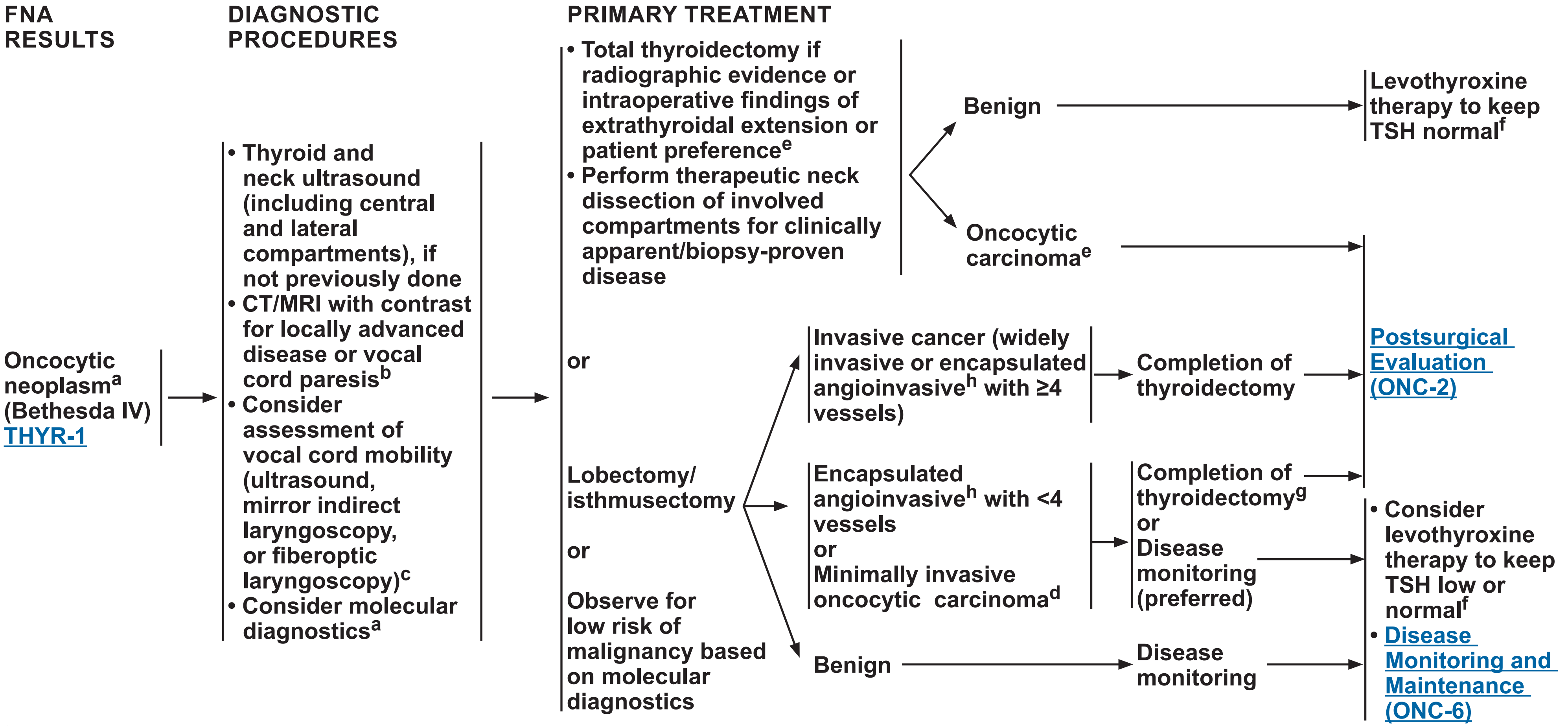
NCCN Guidelines Version 3.2023
Thyroid Carcinoma – Oncocytic Carcinoma
NCCN Evidence Blocks™



FNA RESULTS

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

DIAGNOSTIC PROCEDURES

- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- 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]
- Consider molecular diagnostics[a]

PRIMARY TREATMENT

- Total thyroidectomy if radiographic evidence or intraoperative findings of extrathyroidal extension or patient preference[e]
- Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease

→ Benign → Levothyroxine therapy to keep TSH normal[f]

→ Oncocytic carcinoma[e] → Postsurgical Evaluation (ONC-2)

or

Lobectomy/isthmusectomy

→ Invasive cancer (widely invasive or encapsulated angioinvasive[h] with ≥4 vessels) → Completion of thyroidectomy → Postsurgical Evaluation (ONC-2)

→ Encapsulated angioinvasive[h] with <4 vessels or Minimally invasive oncocytic carcinoma[d] → Completion of thyroidectomy[g] → Postsurgical Evaluation (ONC-2) or Disease monitoring (preferred) → • Consider levothyroxine therapy to keep TSH low or normal[f] • Disease Monitoring and Maintenance (ONC-6)

or

Observe for low risk of malignancy based on molecular diagnostics

→ Benign → Disease monitoring → • Consider levothyroxine therapy to keep TSH low or normal[f] • Disease Monitoring and Maintenance (ONC-6)

---

[a] The diagnosis of oncocytic carcinoma, formerly known as Hurthle 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] 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 oncocytic carcinoma is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

[e] Consider thyroidectomy if tumor >4 cm in diameter.

[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.

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POSTSURGICAL EVALUATION

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

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

- **Resectable** → **Resect, if possible**
  - **No gross residual disease** → **See Consideration for Initial Postoperative RAI Therapy (ONC-3)**
  - **Gross residual disease** →
- **Unresectable**[i] →
  - **TSH + Tg measurement + Tg ab (6–12 wks postoperatively)**
  - **Iodine-123 or iodine-131**[j] **total body radioiodine imaging**[j] **with TSH stimulation (thyroid hormone withdrawal or rhTSH) (category 2B)**
    - **RAI uptake absent**[l,m] →
      - **Monitoring of residual disease**
      - **or**
      - **Consider EBRT if disease is threatening vital structures**[k]
      - **or**
      - **Consider RAI therapy**[k]
    - **RAI uptake present**[l] **or No RAI imaging performed** →
      - **RAI therapy (preferred)**[k]
      - **Post-treatment iodine-131 whole body imaging**
      - **TSH-stimulated Tg**
      - **Consider EBRT**[k]
  - **For viscerally invasive disease or rapid progression, upfront EBRT, neoadjuvant therapy may be most appropriate**[j] →
    - **TSH + Tg measurement + Tg ab (6–12 wks postoperatively)**
    - **Iodine-123 or iodine-131**[j] **total body radioiodine imaging with TSH stimulation (thyroid hormone withdrawal and rhTSH) (category 2B)**
      - **RAI uptake absent**[l,m] →
        - **Monitoring of residual disease**
        - **or**
        - **Consider RAI therapy**[k]
        - **or**
        - **Consider systemic therapy (ONC-9)**
      - **RAI uptake present**[l] **or No RAI imaging performed** →
        - **RAI therapy (preferred)**[k]
        - **Post-treatment iodine-131 whole body imaging**
        - **TSH-stimulated Tg**

→
- **Suppress TSH with levothyroxine**[f]
- **Disease Monitoring and Maintenance (ONC-6)**

---

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

[i] For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.

[j] If considering dosimetry, iodine-131 is the preferred agent.

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

[l] If higher than expected uptake (residual thyroid uptake or distant metastasis), change dose accordingly.

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

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CLINICOPATHOLOGIC FACTORS[n]

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 or stimulated Tg <2 ng/mL[o]
- Negative postoperative ultrasound, if done[p]

→ **RAI not typically indicated (ONC-6)**

RAI selectively recommended (if any present):
- Largest primary tumor 2–4 cm
- Minor vascular invasion(<4 foci)
- Cervical lymph node metastases
- 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 (ONC-4)**

RAI recommended (if any present):
- Significant N1b disease
- Gross extrathyroidal extension[q]
- Primary tumor >4 cm
- Extensive vascular invasion (≥4 foci)
- Postoperative unstimulated Tg >10 ng/mL[o,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 not amenable to RAI therapy → **ONC-9**

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

---

[n] A majority of oncocytic carcinoma are non–iodine-avid, particularly for high-risk disease that is negative on iodine-123/iodine-131 imaging. A negative post-therapy scan, especially done without single-photon emission computerized tomography (SPECT), will likely miss distant structural disease. If Tg is high and/or pathology is high risk, FDG-PET is indicated.

[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.

[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.

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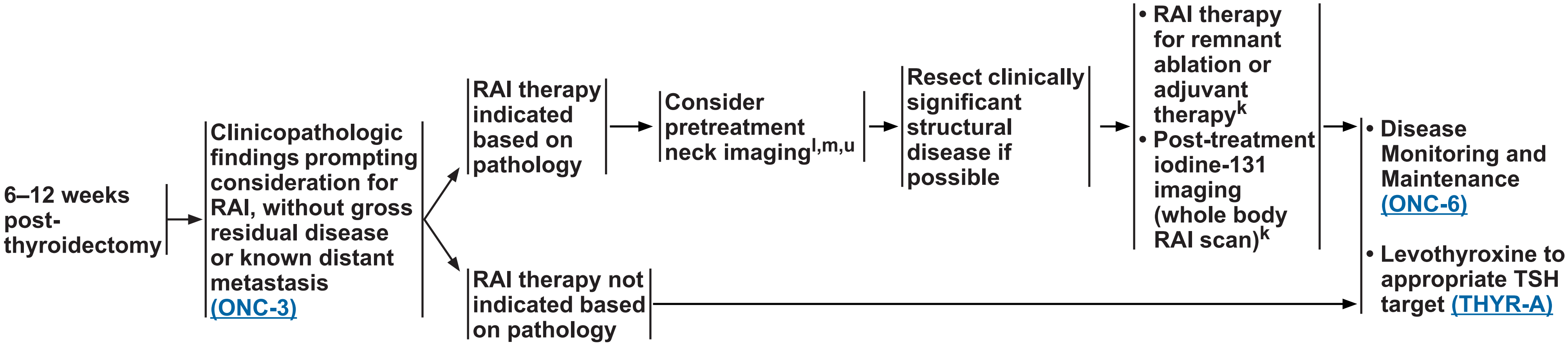
RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



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

→ **RAI therapy indicated based on pathology** → **Consider pretreatment neck imaging**[l,m,u] → **Resect clinically significant structural disease if possible** →
- **RAI therapy for remnant ablation or adjuvant therapy**[k]
- **Post-treatment iodine-131 imaging (whole body RAI scan)**[k]

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

→ **RAI therapy not indicated based on pathology** →
- **Disease Monitoring and Maintenance (ONC-6)**
- **Levothyroxine to appropriate TSH target (THYR-A)**

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

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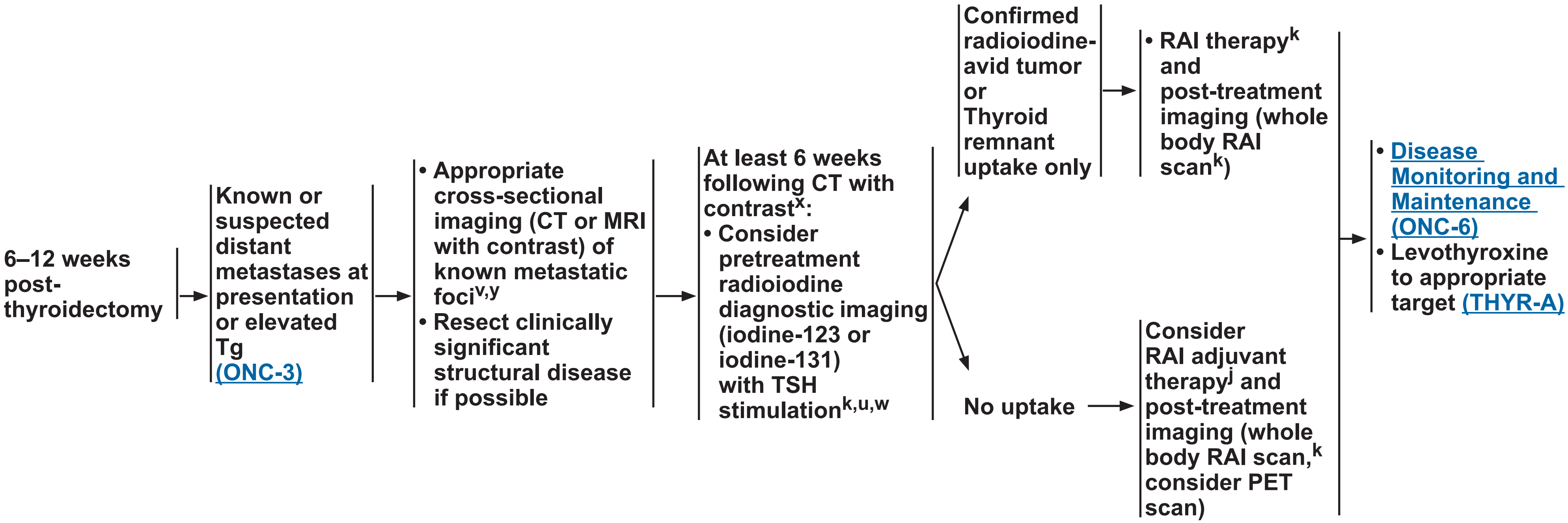
KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



6–12 weeks post-thyroidectomy → 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[v,y]
- Resect clinically significant structural disease if possible

→ At least 6 weeks following CT with contrast[x]:
- Consider pretreatment radioiodine diagnostic imaging (iodine-123 or iodine-131) with TSH stimulation[k,u,w]

→ Confirmed radioiodine-avid tumor or Thyroid remnant uptake only →
- RAI therapy[k] and post-treatment imaging (whole body RAI scan[k])

→ No uptake → Consider RAI adjuvant therapy[j] and post-treatment imaging (whole body RAI scan,[k] consider PET scan)

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

---

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

[u] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative 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.

[v] To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or EBRT) to prevent invasion/compression.

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

[x] Consider 24-hour urine iodine.

[y] If suspicion of pulmonary metastasis, chest CT can be done without contrast.

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Total thyroidectomy without RAI →
- Physical examination
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→ Abnormal imaging and/or rising Tg → Biopsy of suspicious areas on imaging (consider Tg washout) → Recurrent disease (ONC-8)

→ No evidence of disease →
- Physical examination
- TSH (goal based on risk stratification)
- Tg measurement and Tg ab annually if stable
- Neck ultrasound annually, and then every 3–5 years if imaging and Tg/Tg ab stable
- NCCN Guidelines for Survivorship

→ Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)

Total thyroidectomy with RAI (ONC-7)

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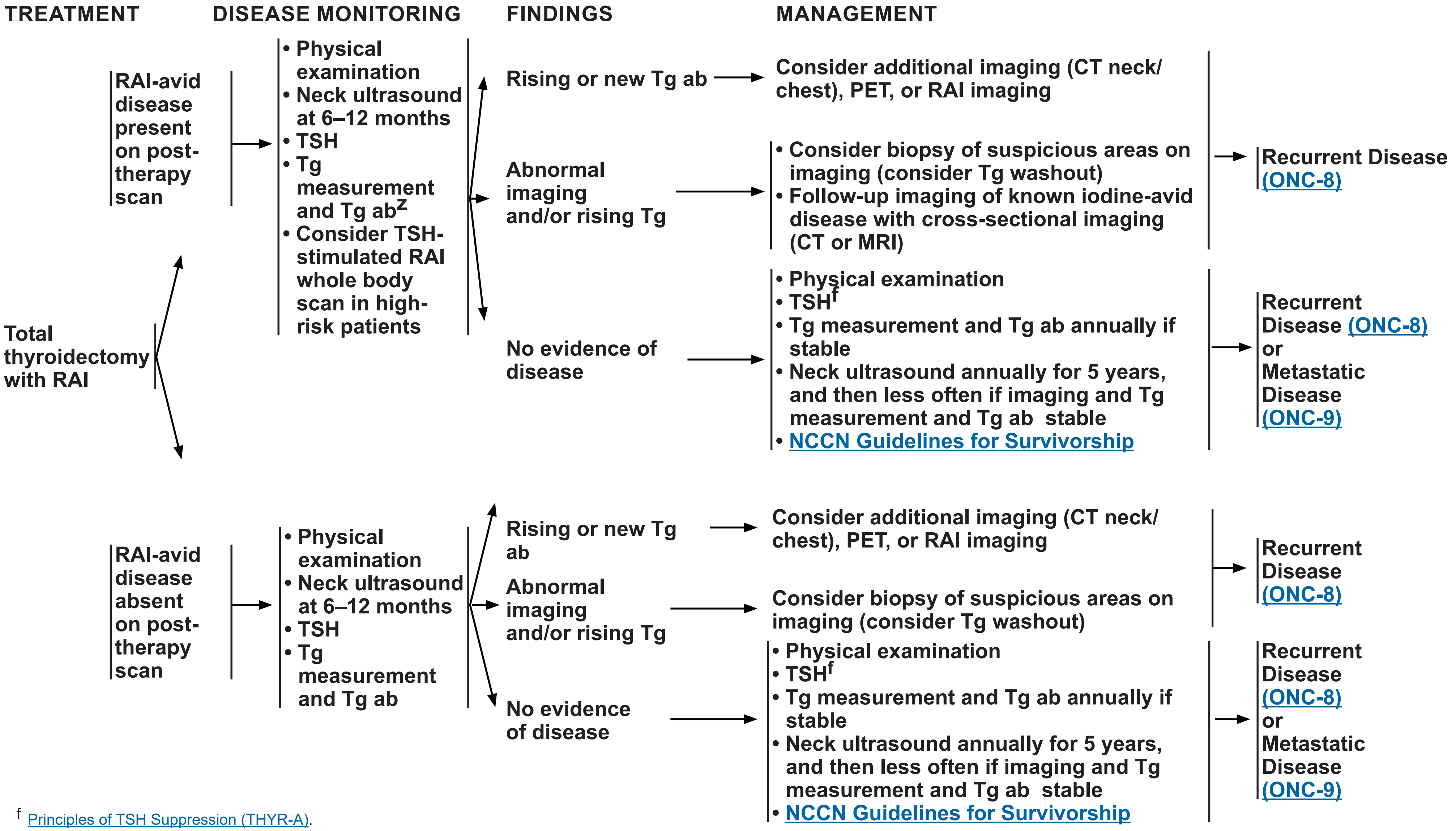

TREATMENT | **DISEASE MONITORING** | **FINDINGS** | **MANAGEMENT**

Total thyroidectomy with RAI

RAI-avid disease present on post-therapy scan →
- Physical examination
- Neck ultrasound at 6–12 months
- TSH
- Tg measurement and Tg ab[z]
- Consider TSH-stimulated RAI whole body scan in high-risk patients

Rising or new Tg ab → Consider additional imaging (CT neck/chest), PET, or RAI imaging

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 (ONC-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
- NCCN Guidelines for Survivorship

→ Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)

RAI-avid disease absent on post-therapy scan →
- Physical examination
- Neck ultrasound at 6–12 months
- TSH
- Tg measurement and Tg ab

Rising or new Tg ab → Consider additional imaging (CT neck/chest), PET, or RAI imaging

Abnormal imaging and/or rising Tg → Consider biopsy of suspicious areas on imaging (consider Tg washout)

→ Recurrent Disease (ONC-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
- NCCN Guidelines for Survivorship

→ Recurrent Disease (ONC-8) or Metastatic Disease (ONC-9)

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

[z] 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.

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RECURRENT DISEASE

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

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

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

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

Locoregional recurrence → **Consider iodine total body scan** →

Surgery (preferred) if resectable[cc]
and
Consider radioiodine treatment,[bb] if 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 of Metastatic Disease 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[k]**
and/or
Local therapies when available[dd]
and/or
ONC-9 if not amenable to RAI

---

[f] Principles of TSH Suppression (THYR-A).
[k] Principles of Radiation and RAI Therapy (THYR-C).

[aa] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 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.
[bb] The administered activity of RAI therapy should be adjusted for pediatric patients. Principles of Radiation and RAI Therapy (THYR-C).
[cc] Preoperative vocal cord assessment, if central neck recurrence.
[dd] Ethanol ablation, cryoablation, RFA, etc.

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

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

→

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

→

Unresectable locoregional recurrent/persistent disease

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

→

- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - ◊ **Lenvatinib (category 1)[ee]**
  - **Other Recommended Regimens**
    - ◊ **Sorafenib (category 1)[ee]**
  - **Useful in Certain Circumstances**
    - ◊ **Cabozantinib if progression after lenvatinib and/or sorafenib**
    - ◊ **Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - ◊ **Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - ◊ **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
    - ◊ **Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - ◊ **Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ff,gg]**
- **Consider resection of distant metastases and/or RT[k] or other local therapies[dd] when available to metastatic lesions if progressive and/or symptomatic (Locoregional disease, ONC-8)**
- **Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[ee] (ONC-6)**
- **Best supportive care, NCCN Guidelines for Palliative Care**

Bone metastases (ONC-10)

CNS metastases (ONC-11)

See Evidence Blocks on ONC-9A

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[f] Principles of TSH Suppression (THYR-A).
[k] Principles of Radiation and RAI Therapy (THYR-C).
[dd] Ethanol ablation, cryoablation, RFA, etc.
[ee] Kinase inhibitor therapy may not be approriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy (THYR-B).
[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.
[gg] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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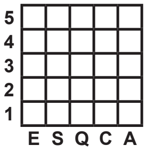

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

EVIDENCE BLOCKS FOR IODINE-REFRACTORY RECURRENT, PERSISTENT, OR METASTATIC ONCOCYTIC THYROID CARCINOMA

Preferred Regimen	
Lenvatinib	
Other Recommended Regimen	
Sorafenib	
Useful in Certain Circumstances	
Cabozantinib (if progression after lenvatinib and/or sorafenib)	
Larotrectinib (for *NTRK* gene fusion-positive tumors)	
Entrectinib (for *NTRK* gene fusion-positive tumors)	
Pralsetinib (for *RET*-fusion positive tumors)	
Selpercatinib (for *RET*-fusion positive tumors)	
Pembrolizumab (for TMB-H tumors)	
Pembrolizumab (MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)	
Dabrafenib/trametinib (for *BRAF* V600E mutation)	

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

Bone metastases →

- **Consider surgical palliation and/or RT[k]/other local therapies[dd] when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage**
- **Consider embolization or other interventional procedures as alternatives to surgical resection/RT in select cases[k]**
- **Consider intravenous bisphosphonate or denosumab[ii]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[gg] (ONC-6)**
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **◊ Lenvatinib (category 1)[ee]**
  - **Other Recommended Regimens**
    - **◊ Sorafenib (category 1)[ee]**
  - **Useful in Certain Circumstances**
    - **◊ Cabozantinib if progression after lenvatinib and/or sorafenib**
    - **◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - **◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - **◊ Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
    - **◊ Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - **◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ee,ff,gg]**
- **Best supportive care, NCCN Guidelines for Palliative Care**

---

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

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

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

[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

[hh] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

[ii] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.

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

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or SRS[k] is preferred**
  or
- **For multiple CNS lesions, consider radiotherapy,[k] including WBRT[k] or SRS,[k] and/or resection in select cases**
- **Consider systemic therapy For progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **Lenvatinib (category 1)[ee,jj,kk]**
  - **Other**
    - **Sorafenib (category 1)[ee,jj,kk]**
  - **Useful in Certain Circumstances**
    - **Cabozantinib if progression after lenvatinib and/or sorafenib**
    - **Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors**
    - **Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors**
    - **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options**
      and/or
    - **Dabrafenib/trametinib for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options**
    - **Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ee,ff,gg,ii]**
- **Best supportive care, NCCN Guidelines for Palliative Care**

---

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

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

[ff] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.

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

[hh] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

[ii] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures.

[jj] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.

[kk] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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CLINICAL PRESENTATION → **DIAGNOSTIC PROCEDURES** → **PRIMARY TREATMENT**

Medullary thyroid carcinoma on FNA by cytology or molecular diagnostics →

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

→ **≥1.0 cm in diameter or bilateral thyroid disease** →

- Total thyroidectomy with bilateral central neck dissection (level VI)
- Therapeutic ipsilateral or bilateral modified neck dissection for clinically or radiologically identifiable disease (levels II–V)
- Consider prophylactic ipsilateral modified neck dissection for high-volume or gross disease in the adjacent central neck
- Consider therapeutic EBRT[h] for grossly incomplete tumor resection when additional attempts at surgical resection have been ruled out
- Adjuvant EBRT is rarely recommended[h]
- Postoperative administration of levothyroxine to normalize TSH

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

→ **<1.0 cm in diameter and unilateral thyroid disease** → **Total thyroidectomy and consider neck dissection (level VI)** → **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* proto-oncogene[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 mutation testing have not yet been received.

[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling. 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] Imaging may be indicated based on high burden of disease, calcitonin >500 pg/mL, or elevated CEA levels.

[g] Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor. Principles of Cancer Risk Assessment and Counseling (THYR-E).

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

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CLINICAL PRESENTATION

Medullary thyroid carcinoma diagnosed after initial thyroid surgery[i]

ADDITIONAL WORKUP

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

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

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

MANAGEMENT

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[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling. 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* mutation 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.

CLINICAL PRESENTATION | **ADDITIONAL WORKUP** | **PRIMARY TREATMENT**

Germline mutation of *RET* proto-oncogene[a,c]

→ **Multiple endocrine neoplasia (MEN2B) (*RET* mutations)**[k]

→ Additional workup:
- **Basal serum calcitonin level**[l]
- **CEA**
- **Pheochromocytoma screening**[b,m]
- **Central and lateral neck compartments ultrasound,**[n] **if not previously done**
- **Consider neck CT with contrast if indicated**

→ Primary treatment:
- **Total thyroidectomy during the first year of life or at diagnosis**[a]
- **Therapeutic neck dissection as indicated; consider prophylactic bilateral 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* mutations)**[k]

→ Additional workup:
- **Basal serum calcitonin level**[l]
- **CEA**
- **Pheochromocytoma screening**[b,m]
- **Serum calcium + parathyroid hormone**[n]
- **Central and lateral neck compartments ultrasound,**[n] **if not previously done**
- **Consider neck CT with contrast if indicated**

→ **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 treated appropriately before proceeding to the next step on the pathway in patients for whom results from RET mutation testing have not yet been received.

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

[k] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other *RET* mutations associated with MEN2A or FMTC are generally moderate risk. Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, et al. J Clin Endocrinol Metab 2001;86:5658-5671; and American Thyroid Association Guidelines Task Force. Wells SA 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* mutations (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.

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

CLINICAL PRESENTATION

MEN2A/FMTC (RET mutations)[a,c,k] →

PRIMARY TREATMENT

No primary hyperparathyroidism →

- **Total thyroidectomy by age 5[a,k] or when mutation identified[a] (if mutation identified at older age)**
- **Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin[o] or CEA test or ultrasound identified thyroid or nodal abnormality**
- **Consider prophylactic ipsilateral modified neck dissection if there is high-volume or gross disease in the adjacent central neck**
- **Consider more extensive lymph node dissection (levels II–V) if tumor(s) >1.0 cm or central node(s) positive**
- **Postoperative administration of levothyroxine to normalize TSH**

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

Primary hyperparathyroidism →

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

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

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[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.

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

[k] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other *RET* mutations associated with MEN2A or FMTC are generally moderate risk. Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, et al. J Clin Endocrinol Metab 2001;86:5658-5671; and American Thyroid Association Guidelines Task Force. Wells SA 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.

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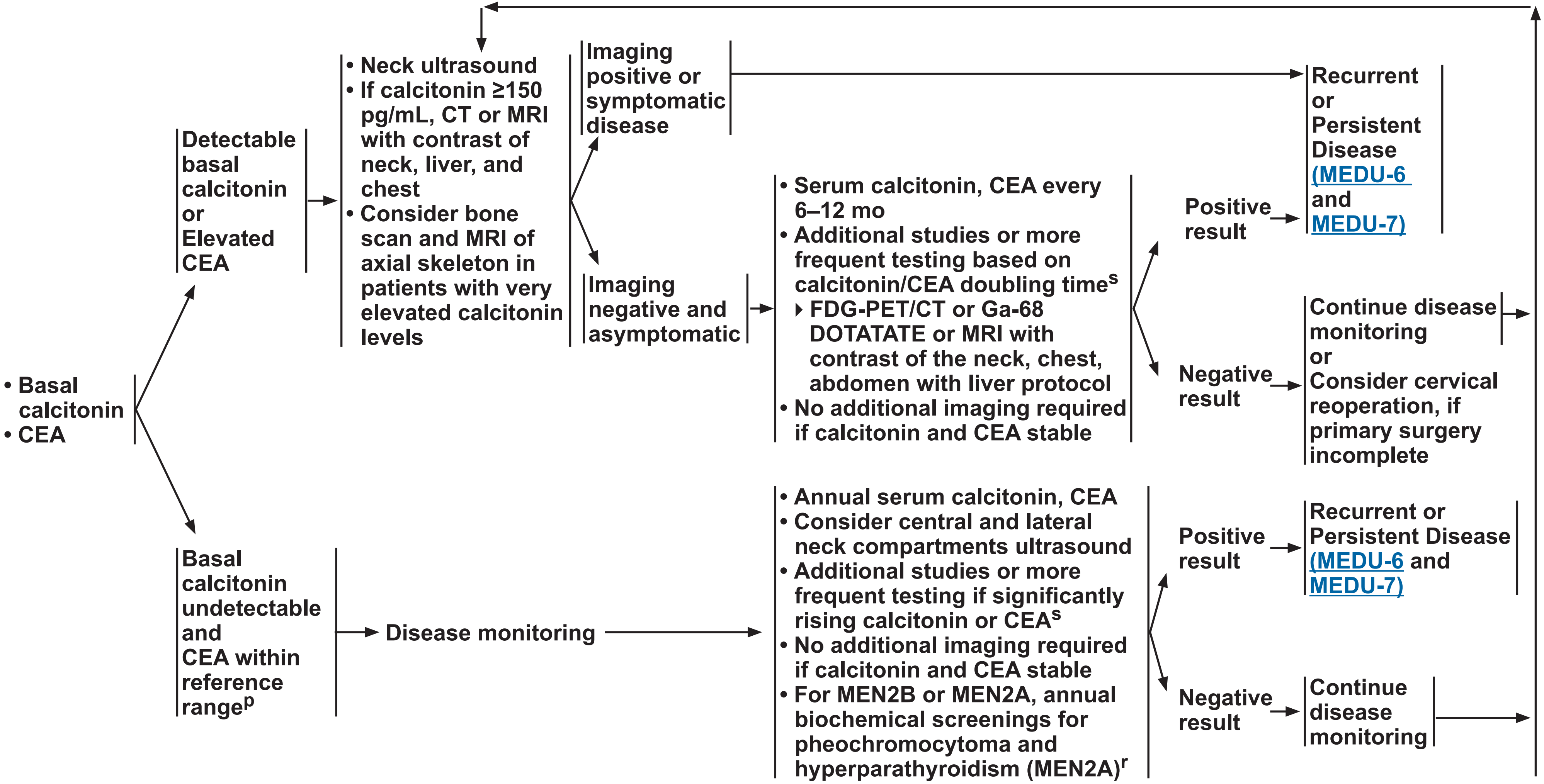
MANAGEMENT 2–3 MONTHS POSTOPERATIVE

DISEASE MONITORING[q]



- Basal calcitonin
- CEA

Detectable basal calcitonin or Elevated CEA →

- Neck ultrasound
- If calcitonin ≥150 pg/mL, CT or MRI with contrast of neck, liver, and chest
- Consider bone scan and MRI of axial skeleton in patients with very elevated calcitonin levels

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

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

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[p] The likelihood of significant residual disease with an undetectable basal calcitonin is very low.

[q] 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.

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RECURRENT OR PERSISTENT LOCOREGIONAL DISEASE | **TREATMENT**

Locoregional →

- **Surgical resection is the preferred treatment modality**
- **EBRT can be considered for unresectable disease or, less commonly, after surgical resection[h]**
- **Consider systemic therapy[t] for unresectable disease that is symptomatic or progressing by RECIST criteria[u,v]**
  - **Preferred Regimens**
    - ◊ **Vandetanib[w] (category 1)**
    - ◊ **Cabozantinib (category 1)**
    - ◊ **Selpercatinib (*RET* mutation-positive)[x]**
    - ◊ **Pralsetinib (*RET* mutation-positive)[x] (category 2B)**
  - **Useful in Certain Circumstances**
    - ◊ **Pembrolizumab (TMB-H [≥10 mut/Mb][x] or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)**
- **Disease monitoring**

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

See Evidence Blocks on MEDU-6A

---

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

[t] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.

[u] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).

[v] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

[w] 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.

[x] Genomic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown. Genomic testing including TMB or RET somatic genotyping in patients who are germline wild-type or germline unknown.

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EVIDENCE BLOCKS FOR RECURRENT OR PERSISTENT LOCOREGIONAL MEDULLARY THYROID CARCINOMA THAT IS UNRESECTABLE AND SYMPTOMATIC OR PROGRESSING

Preferred Regimens	
Vandetanib	
Cabozantinib	
Selpercatinib (for *RET* mutation-positive)	
Pralsetinib (for *RET* mutation-positive)	
Useful in Certain Circumstances	
Pembrolizumab (for TMB-H tumors)	
Pembrolizumab (MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

RECURRENT OR PERSISTENT DISEASE

DISTANT METASTASES

Asymptomatic disease →

- **Disease monitoring**
- **Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy)**
- **Systemic therapy[t] if not resectable and progressing by RECIST criteria[u,v]**
  - **Preferred Regimens**
    - ◊ **Vandetanib[u,w] (category 1)**
    - ◊ **Cabozantinib (category 1)**
    - ◊ **Selpercatinib (*RET* mutation-positive)[x]**
    - ◊ **Pralsetinib (*RET* mutation-positive)[x] (category 2B)**
  - **Useful in Certain Circumstances**
    - ◊ **Pembrolizumab (TMB-H [≥10 mut/Mb][x] or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)**

→ **Progressive disease, pathway below**

Symptomatic disease or Progression[t] →

- **Systemic therapy or clinical trial**
  - **Preferred Regimens**
    - ◊ **Vandetanib (category 1)[y]**
    - ◊ **Cabozantinib (category 1)[y]**
    - ◊ **Selpercatinib (*RET* mutation-positive)[x]**
    - ◊ **Pralsetinib (*RET* mutation-positive)[x] (category 2B)**
  - **Other Recommended Regimens**
    - ◊ **Consider other small-molecule kinase inhibitors[z]**
    - ◊ **Dacarbazine (DTIC)-based chemotherapy[aa]**
  - **Useful in Certain Circumstances**
    - ◊ **Pembrolizumab (TMB-H [≥10 mut/Mb][x]or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)**
- **EBRTfor local symptoms[h]**
- **Consider intravenous bisphosphonate or denosumab[bb] therapy for bone metastases**
- **Consider palliative resection, ablation (eg, RFA, embolization, other regional therapy), or other regional treatment**
- **Best supportive care, NCCN Guidelines for Palliative Care**

See Evidence Blocks on MEDU-7A

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

[t] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.

[u] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).

[v] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

[w] 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.

[x] Genomic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown. Genomic testing including TMB or RET somatic genotyping in patients who are germline wild-type or germline unknown.

[y] Clinical benefit can be seen in both sporadic and FMTC.

[z] 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.

[aa] Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine or fluorouracil/dacarbazine alternating with flurouracil/streptozocin.

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

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EVIDENCE BLOCKS FOR RECURRENT OR PERSISTENT DISTANT METASTATIC MEDULLARY THYROID CARCINOMA

Preferred Regimens	
Vandetanib	
Cabozantinib	
Selpercatinib (for *RET* mutation-positive)	
Pralsetinib (for *RET* mutation-positive)	
Other Recommended Regimens	
Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine	
Fluorouracil/dacarbazine alternating with fluorouracil/streptozocin	
Useful in Certain Circumstances	
Pembrolizumab (for TMB-H tumors)	
Pembrolizumab (MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options)	

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FNA OR CORE BIOPSY FINDING[a]

Anaplastic thyroid carcinoma (ATC) →

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
- Fluorodeoxyglucose (FDG)-PET/CT or MRI
- In case of airway invasion, bronchoscopy
- Molecular testing for actionable mutations[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

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[a] Consider core or open biopsy if FNA is “suspicious” for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and lymphoma.

[b] Molecular testing should include BRAF, NTRK, ALK, RET, MSI, dMMR, and tumor mutational burden.

[c] Preoperative evaluations need to be completed as quickly as possible and involve integrated decision-making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.

[d] Staging (ST-1).

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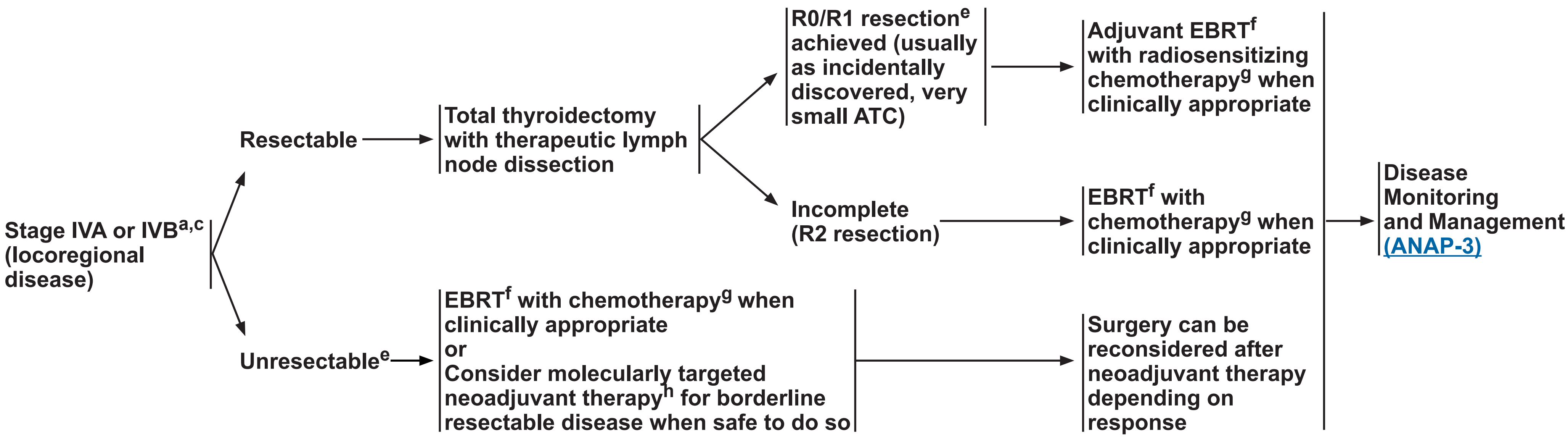
STAGE[d] **TREATMENT**



- **Stage IVA or IVB[a,c] (locoregional disease)**
  - **Resectable** → **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[g] when clinically appropriate** → **Disease Monitoring and Management (ANAP-3)**
    - **Incomplete (R2 resection)** → **EBRT[f] with chemotherapy[g] when clinically appropriate** → **Disease Monitoring and Management (ANAP-3)**
  - **Unresectable[e]** → **EBRT[f] with chemotherapy[g] when clinically appropriate or Consider molecularly targeted neoadjuvant therapy[h] for borderline resectable disease when safe to do so** → **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, squamous cell carcinoma, and lymphoma.

[c] Preoperative evaluations need to be completed as quickly as possible and involve integrated decision-making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.

[d] 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. Staging (ST-1) for definitions of R0/R1/R2.

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

[g] Adjuvant/Radiosensitizing Chemotherapy Regimens for Anaplastic Thyroid Carcinoma (ANAP-A [1 of 3]).

[h] Regimens that may be used for neoadjuvant therapy include dabrafenib/trametinib for *BRAF* V600E mutations; selpercatinib or pralsetinib for RET gene fusion-positive tumors; and larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive tumors.

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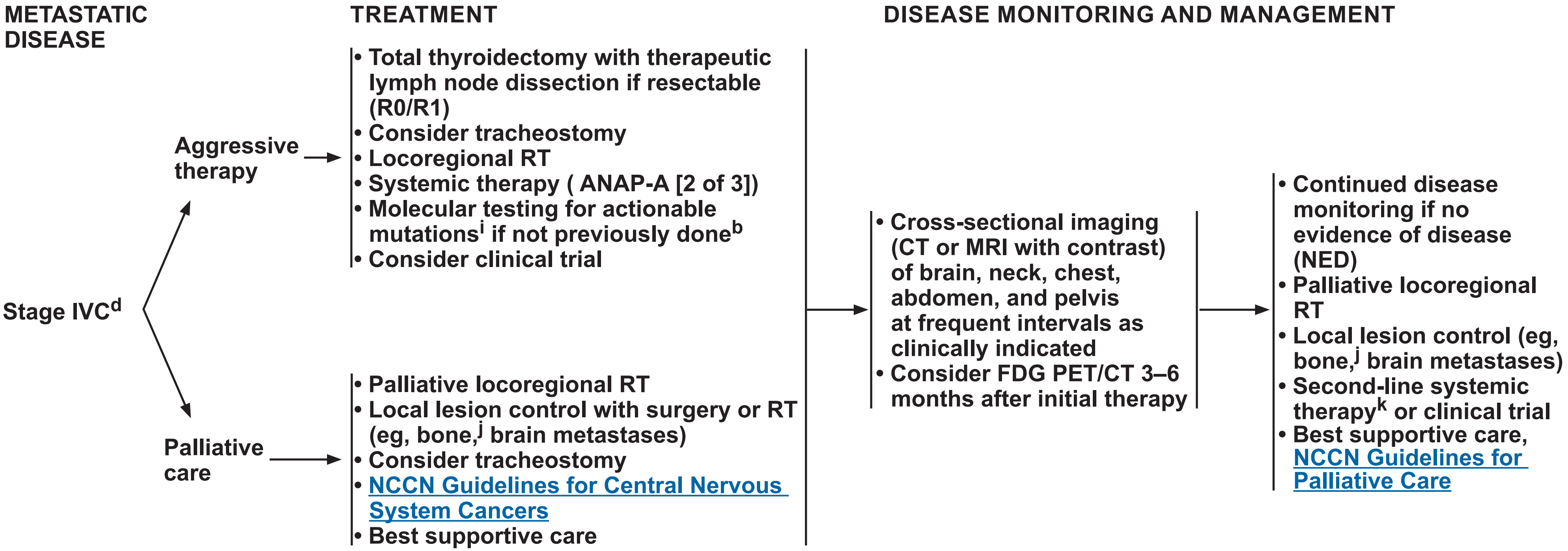

METASTATIC DISEASE

Stage IVC[d]

Aggressive therapy →

TREATMENT

- Total thyroidectomy with therapeutic lymph node dissection if resectable (R0/R1)
- Consider tracheostomy
- Locoregional RT
- Systemic therapy (ANAP-A [2 of 3])
- Molecular testing for actionable mutations[i] if not previously done[b]
- Consider clinical trial

Palliative care →

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

→

DISEASE MONITORING AND MANAGEMENT

- 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,[j] brain metastases)
- Second-line systemic therapy[k] or clinical trial
- Best supportive care, NCCN Guidelines for Palliative Care

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[b] Molecular testing should include BRAF, NTRK, ALK, RET, MSI, dMMR, and tumor mutational burden.

[d] Staging (ST-1).

[i] Consider dabrafenib/trametinib if *BRAF* V600E mutation positive (Subbiah V, et al. J Clin Oncol 2018;36:7-13); larotrectinib or entrectinib if *NTRK* gene fusion positive (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282); selpercatinib or pralsetinib if *RET* fusion positive (Wirth L, et al. Presented at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27-October 1, 2019. Oral presentation.); or pembrolizumab for TMB-H (Marabelle A, et al. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019).

[j] Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

[k] Systemic Therapy Regimens for Metastatic Disease (ANAP-A [2 of 3]).

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SYSTEMIC THERAPY

Adjuvant/Radiosensitizing Chemotherapy Regimens[1]		
<u>Other Recommended Regimens</u>		
Paclitaxel/carboplatin	Paclitaxel 50 mg/m^2 IV, carboplatin area under the curve (AUC) 2 IV	Weekly
Docetaxel/doxorubicin	Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Weekly
Paclitaxel	30–60 mg/m^2 IV	Weekly
Docetaxel	20 mg/m^2 IV	Weekly

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

See Evidence Blocks on ANAP-A (EB-1)

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[1] Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021;31:337-386.

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EVIDENCE BLOCKS FOR ADJUVANT/RADIOSENSITIZING CHEMOTHERAPY FOR ANAPLASTIC THYROID CARCINOMA

Other Recommended Regimens	
Paclitaxel/carboplatin + RT	
Docetaxel/doxorubicin + RT	
Paclitaxel + RT	
Docetaxel + RT	

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SYSTEMIC THERAPY

Systemic Therapy Regimens for Metastatic Disease		
Preferred Regimens		
Dabrafenib/trametinib[2] (*BRAF* V600E mutation positive)	**Dabrafenib 150 mg PO** **and** **Trametinib 2 mg PO**	**Twice daily** **Once daily**
Larotrectinib[3] (*NTRK* gene fusion positive)	**100 mg PO**	**Twice daily**
Entrectinib[4] (*NTRK* gene fusion positive)	**600 mg PO**	**Once daily**
Pralsetinib[5] (*RET* gene fusion-positive)	**400 mg PO**	**Once daily**
Selpercatinib[6] (*RET* gene fusion-positive)	**120 mg PO (<50 kg)** **or** **160 mg PO (≥50 kg)**	**Twice daily**
Other Recommended Regimens		
Paclitaxel[8]	**60–90 mg/m^2 IV** **or** **135–200 mg/m^2**	**Weekly** **Every 3–4 weeks**
Doxorubicin[8]	**20 mg/m^2 IV** **or** **60–75 mg/m^2 IV**	**Weekly** **Every 3 weeks**
Paclitaxel/carboplatin[1] **(category 2B)**	**Paclitaxel 60–100 mg/m^2 IV, carboplatin AUC 2 IV** **or** **Paclitaxel 135–175 mg/m^2 IV, carboplatin AUC 5–6 IV**	**Weekly** **Every 3–4 weeks**
Docetaxel/doxorubicin[1] **(category 2B)**	**Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (with G-CSF)** **or** **Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV**	**Every 3–4 weeks** **Weekly**
Useful in Certain Circumstances		
Doxorubicin/cisplatin[8]	**Doxorubicin 60 mg/m^2 IV, cisplatin 40 mg/m^2 IV**	**Every 3 weeks**
Pembrolizumab[7] (TMB-H [≥10 mut/Mb])	**200 mg IV** **or** **400 mg IV**	**Every 3 weeks** **Every 6 weeks**

See Evidence Blocks on ANAP-A (EB-2)

References on ANAP 3 of 3

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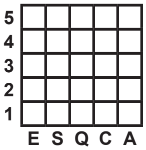

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

EVIDENCE BLOCKS FOR SYSTEMIC THERAPY FOR METASTATIC ANAPLASTIC THYROID CARCINOMA

Preferred Regimens	
Dabrafenib/trametinib **(*BRAF* V600E mutation-positive disease)**	
Larotrectinib (for *NTRK* gene fusion-positive tumors)	
Entrectinib (for *NTRK* gene fusion-positive tumors)	
Pralsetinib (for *RET*-fusion positive tumors)	
Selpercatinib (for *RET*-fusion positive tumors)	
Other Recommended Regimens	
Paclitaxel/carboplatin	
Docetaxel/doxorubicin	
Paclitaxel	
Doxorubicin	
Useful in Certain Circumstances	
Pembrolizumab (for TMB-H tumors)	
Doxorubicin/cisplatin	

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SYSTEMIC THERAPY REFERENCES

[1] Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-1139.
[2] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36:7-13.
[3] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.
[4] Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
[5] Subbiah V, Hu MI, Gainor JF, et al. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020.
[6] Wirth L, Sherman E, Drilon A, et al. Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET-altered thyroid cancers. Presented at the Annual Meeting of the European Society for Medical Oncology; September 27-October 1, 2019; Barcelona, Spain. Oral presentation.
[7] Marabelle A, Fakih MG, Lopez J, et al. Association of tumor mutational burden with outcomes in patients with select advanced solid tumors treated with pembrolizumab in KEYNOTE-158. Presented at the Annual Meeting of the European Society for Medical Oncology; September 30, 2019; Barcelona, Spain.
[8] Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021;31:337-386.

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PRINCIPLES OF THYROID-STIMULATING HORMONE (TSH) SUPPRESSION

- **Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or 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 calcium (1200 mg/day) and vitamin D (1000 IU).**

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PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA[1-7]

- **Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic MTC and in radioiodine-refractory differentiated thyroid cancer (DTC).**

- **When considering kinase inhibitor therapy for individual patients, several factors should be considered.**
  - **Kinase inhibitor therapy can be associated with improved progression-free survival, but is not curative.**
  - **Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.**
  - **The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.**

- **The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have drug-induced side effects.**

- **Optimal management of kinase inhibitor side effects is essential. Where available, guidelines outlining the management of the dermatologic, hypertensive, and gastrointestinal side effects of kinase inhibitors can be used; side effects have been fatal. In addition, dose modification may be required, including dose holds and dose reductions.**

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

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
IODINE-131 ADMINISTRATION

General Principles

Patients may be withdrawn from thyroid hormone to allow adequate elevation of TSH (>30 mU/l),[1] or prepared using 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. 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 .[2,3]
- Regardless of preparation method, an iodine-restricted diet is recommended for 7–14 days prior to iodine-131 therapy. A review of recent clinical history is advised to confirm the absence of recent iodinated contrast administration, amiodarone therapy over the past year, or long-acting iodine contaminants. Dietary supplements such as fish oil and daily multivitamins containing iodine should also be withheld over this period. Most common contrast media for CT require a 2-month period between contrast administration and iodine scintigraphy for adequate washout. If available, a 24-hour urine collection should be performed to confirm a normal free iodine (<100 mcg/24 h) prior to the initiation of the iodine-restricted diet. The diet involves a 10- to 14-day reduction in intake of iodized salt, seafood, and dairy products with the intention of optimizing the sensitivity of diagnostic 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 radioiodine therapy.
- Adherence to all local, state, and national regulatory guidelines including signed informed consent and signed written directive from an authorized user should be confirmed.
- Written guidelines for minimizing exposure to others should be provided for patient signature, as per national and state regulatory requirements.
- Pre-treatment radioiodine imaging may be considered and a post-treatment iodine-131 whole body scan should be performed in all cases.
- Pre-therapy whole body scans may be obtained using 2–4 mCi iodine-123 or 1–2 mCi iodine-131. Iodine-123 avoids stunning and has favorable imaging characteristics. Low activity (1–3 mCi) iodine-131 minimizes stunning and has a longer physical half-life that will permit delayed imaging to improve lesion detection while permitting dosimetry in cases where dose maximization is considered. If iodine-131 is utilized then the time between the scanning and therapy doses should ideally by <48 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: 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).[29]

References on THYR-C 5 of 5

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
IODINE-131 ADMINISTRATION

Administered Activity

See special circumstances below for pediatric dose adjustment.

- Remnant ablation:
  - 30–50 mCi
    - ◊ If RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, in the absence of other adverse pathologic, laboratory, or imaging features, 30–50 mCi of iodine-131 is recommended (category 1) following either thyrotropin alfa stimulation or thyroid hormone withdrawal. This dose of 30–50 mCi may also be considered (category 2B) for patients with T1b/T2 (1–4 cm) with small-volume N1a disease (fewer than 5 lymph node metastases <2 mm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.[4,5]
- Adjuvant therapy:
  - 50–150 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)[6]

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 (<100 mcg/24 hours) and allow for optimal RAI uptake.[7,8]
  - Consider measurement of 24-hour urine iodine to confirm a normal free iodine prior to preparing for dosing.
- Breastfeeding patients:
  - Wait 3–6 months after cessation of lactation or with normalization of serum prolactin levels.
  - Complete cessation of breastfeeding after iodine-123 or iodine-131 administration for the current infant. There should be no increased risk to mother or infant for breastfeeding with subsequent births assuming no radioiodine is administered around the subsequent birth/breastfeeding period.[9]
- Decreased GFR/end-stage renal disease (ESRD)/hemodialysis:
  - Special consideration to administered dose, and timing with respect to dialysis to maximize therapeutic effect and minimize non-thyroid uptake/exposure[10]
  - Multidisciplinary involvement including close monitoring by radiation safety to coordinate administration, monitoring, and minimization of exposure to others
- 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.

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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[11-14]
  - GTV includes gross primary disease and involved lymph nodes (determined on contrast-enhanced CT, MRI, and/or FDG-PET, assuming obtaining these studies does not delay start of treatment).
  - High-risk CTV may include involved lymph node regions and postoperative bed in the case of partial or complete debulking surgery.
  - Elective nodal regions may be included in low-dose CTV if extended-field RT is used.
  - GTV should be expanded by 0.5–1.5 cm to CTV.
  - PTV margins of 0.3–0.5 cm should be added to CTV, depending on technique and image guidance used.

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY
EXTERNAL BEAM RADIATION THERAPY

Dose and Fractionation

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

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

- Adjuvant RT for high-risk disease (after R1 resection)
  - Microscopic disease (thyroid bed, involved resected lymph node regions): 60–66 Gy in 1.8–2 Gy per fraction
  - Elective nodal regions: 50–56 Gy in 1.6–2 Gy per fraction
- Salvage RT after R2 resection or inoperable patients
  - Gross disease: 66–70 Gy in 1.8–2 Gy per fraction
  - Microscopic disease (thyroid bed, involved resected lymph node regions): 60–66 Gy in 1.8–2 Gy per fraction
  - Elective nodal regions: 50–56 Gy in 1.6–2 Gy per fraction
- Palliative RT of metastases
  - Bony or soft-tissue metastases[22]
    - ◊ For patients with oligometastatic disease and good performance status consider higher doses (45–60 Gy) in 1.8–2 Gy daily fractions, or 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 (NCCN Guidelines for Central Nervous System Cancers BRAIN-C 5 of 8)
    - ◊ ≤4 metastases – consider SRS either following surgical resection or as monotherapy
    - ◊ Multiple metastases:
      - – Consider enrollment on clinical trial for SRS versus WBRT (with or without hippocampal avoidance)
      - – WBRT – 30 Gy in 10 daily fractions; consider 45 Gy in 1.8 Gy daily fractions for good performance status[23,24]

Anaplastic Thyroid Cancer

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

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PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY

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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 histology such as tall cell variant; invasion of recurrent laryngeal nerve, trachea, or esophagus; visible extrathyroidal extension; regional or distant metastases; tumor near posterior capsule.**
- **Patient characteristics: Unable or unwilling to follow-up for surveillance.**
- **Physician characteristics: Lack of experience and confidence in the use of neck ultrasound.**

Surveillance Strategy

- **Neck ultrasound, with inclusion of thyroid and lymph node regions, should be performed every 6 months for 1–2 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.**

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[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.

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

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

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

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

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm or less in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension beyond the strap muscle
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

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

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

Table 3. Definitions for T, N, M

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm or less in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor ≥4 cm or with extrathyroidal extension
T3a	Tumor ≥4 cm in greatest dimension limited to the thyroid
T3b	Tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)
T4	Advanced disease
T4a	Moderately advanced disease; tumor of any size with gross extrathyroidal extension into the nearby tissues of the neck, including subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Very advanced disease; tumor of any size with extension toward the spine or into nearby large blood vessels, gross extrathyroidal extension invading the prevertebral fascia, or encasing the carotid artery or mediastinal vessels

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

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

Table 2. AJCC Prognostic Stage Groups

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

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ABBREVIATIONS

ATC	anaplastic thyroid carcinoma
AUC	area under the curve
AUS	atypia of undetermined significance
CEA	carcinoembryonic antigen
CGP	comprehensive genomic profiling
CTV	clinical target volume
CNS	central nervous system
dMMR	mismatch repair deficient
DTC	differentiated thyroid cancer
EBRT	external beam radiation therapy
FDG	fluorodeoxyglucose
FLUS	follicular lesion of undetermined significance
FMTC	familial medullary thyroid carcinoma
FNA	fine-needle aspiration
GFR	glomerular filtration rate
GTV	gross tumor volume
MEN2A	multiple endocrine neoplasia type 2A
MEN2B	multiple endocrine neoplasia type 2B
MSI	microsatellite instability
MTC	medullary thyroid cancer
NIFTP	noninvasive follicular thyroid neoplasm with papillary-like nuclear features
PTC	papillary thyroid carcinoma
PTV	planning target volume
RAI	radioactive iodine
RFA	radiofrequency ablation
rhTSH	recombinant human TSH
RT	radiation therapy
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
TMB-H	tumor mutational burden-high
TSH	thyroid-stimulating hormone
WBRT	whole brain radiation therapy

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Thyroid Carcinoma. Last updated: May 5, 2022.

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Overview

Epidemiology

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

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%.[7] It is estimated that approximately 43,800 new cases of thyroid carcinoma will be diagnosed in the United States in 2022.[8] As with thyroid nodules, thyroid carcinoma occurs two to three times more often in women than in men. Thyroid carcinoma is currently the seventh most common malignancy diagnosed in women.[8] The disease is also diagnosed more often in white North Americans than in African Americans. The main histologic types of thyroid carcinoma are: 1) differentiated (including papillary, follicular, and Hürthle cell); 2) medullary; and 3) anaplastic, which is an aggressive undifferentiated tumor. Of 63,324 patients diagnosed with thyroid carcinoma from 2011 to 2015, 89.8% had papillary carcinoma, 4.5% had follicular carcinoma, 1.8% had Hürthle cell carcinoma, 1.6% had medullary carcinoma, and 0.8% had anaplastic carcinoma.[7] 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] 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 Hürthle cell carcinomas. In 2022, it is estimated that approximately 2230 cancer deaths will occur among persons with thyroid carcinoma in the United States.[8] Thyroid carcinoma occurs more often in women; however, mortality rates are lower for younger women.[7,11-13] Although the estimated incidence of thyroid carcinoma previously increased by an average of ~5% annually between 2004 and 2013, the incidence rate has more recently stabilized, likely due to more conservative indications for thyroid biopsy and the reclassification of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[14] 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).[15-20] However, data show the incidence has increased by varying degrees across all tumor sizes and age groups.[21-30] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[31,32] A cohort study of 2000–2016 data from U.S. cancer registries showed an increase in incidence of aggressive PTC.[33]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma address management for the different types of thyroid carcinomas including papillary, follicular, Hürthle cell, 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Thyroid Carcinoma, an electronic search of the PubMed database was performed to obtain key literature since the previous Guidelines update, using the following search term: thyroid carcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[34]

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing data and recommendations from other organizations, the terms *men*, *male*, *women*, and *female* will be used to be consistent with the cited sources.

Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma can be a challenge, because until recently, few prospective randomized trials of treatment have been done.[35,36] 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.[37] The treatment of choice is surgery, followed by radioactive iodine (RAI) ablation (iodine-131) in selected patients and thyroxine therapy in most patients.

Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma.[38] 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.[39] 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.[40] After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary carcinomas after being exposed to iodine-131 fallout.[41] It became evident that iodine-131 and other short-lived iodine-131s were potent thyroid carcinogens in these children, particularly those younger than 10 years when they were exposed.[42] Iodine deficiency increases the risk for radiation-induced thyroid cancer.[43] 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.[44-46] Iodine deficiency is associated with follicular carcinoma and anaplastic carcinomas.

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. However, evaluating all nodules for malignancy is difficult, because benign nodules are so prevalent and because thyroid carcinoma is so uncommon.[1,47,48] 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.[49] The other 50% are often first noticed by the patient, usually as an asymptomatic nodule.[1,47]

Fine-needle aspiration (FNA) with ultrasound guidance is the procedure of choice for evaluating suspicious thyroid nodules.[3,48,50] 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.[51-54]

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present.[55,56] 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.[56,57] 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.[57] A patient's age and gender also affect the probability of malignancy. Other factors that increase the suspicion of malignancy include: 1) a history of head and neck irradiation; 2) a history of diseases associated with thyroid carcinoma, such as familial adenomatous polyposis (formerly called Gardner 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.[3,58]

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 BI-RADS classification for breast cancer, was published in 2017 and also includes recommendations for management of thyroid nodules based on ultrasound findings.[59] 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.[60] 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 or unsatisfactory biopsy; category II: benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis); category III: atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); category IV: follicular neoplasm or suspicious for follicular neoplasm (includes Hürthle cell neoplasm); category V: suspicious for malignancy; or category VI: malignancy (includes papillary, medullary, anaplastic, or lymphoma). These diagnostic categories for FNA results reflect the 2017 Bethesda

System for Reporting Thyroid Cytopathology.[61] As of the 2021 update to the NCCN Guidelines for Thyroid Carcinoma, management recommendations are no longer provided 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.[62,63]

Molecular diagnostic testing to detect individual mutations (eg, *BRAF* V600E, *RET/PTC*, *RAS*, *PAX8/PPAR* [peroxisome proliferator-activated receptor] 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.[64-72] The *BRAF* V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation.[73] Some studies have linked the *BRAF* V600E mutation to poor prognosis, especially when occurring with *TERT* promoter mutation.[74-77] The choice of the precise molecular test depends on the cytology and the clinical question being asked.[78-81] Indeterminate groups include: 1) follicular or Hürthle cell neoplasms (Bethesda IV); and 2) AUS/FLUS (Bethesda III).[82-84] The NCCN Panel recommends consideration of molecular diagnostic testing for these indeterminate groups.[85,86]

Historically, studies have shown that molecular diagnostics do not perform well for Hürthle cell neoplasms.[83,87,88] More recently, modern genomic classifiers have shown promise for diagnosis of Hürthle cell-containing specimens, with sensitivity values ranging from 88.9% to 92.9% and specificity values ranging from 58.8% to 69.3% for detecting Hürthle cell cancers.[89,90] 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.

A minority of panelists expressed concern regarding active nodule surveillance of follicular lesions because they were perceived as potentially pre-malignant lesions with a very low, but unknown, malignant potential if not surgically resected (leading to recommendations for either nodule surveillance or considering lobectomy in lesions classified as benign by molecular testing). 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.[3,59] A systematic review including 27 studies that evaluated repeat FNA in AUS/FLUS nodules showed that 48% (95% CI, 43%–54%) of nodules were reclassified as benign, with a negative predictive value (NPV) greater than 96%.[91] FNA may be repeated for AUS/FLUS, 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 pre-test probability of disease associated with the various FNA cytology groups. Furthermore, in the cytologically indeterminate groups, the risk of malignancy from FNA can vary widely between institutions.[61,92] 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.[86,93]

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of medullary carcinoma.[94] Hürthle cell neoplasms can sometimes mimic medullary carcinoma cytologically and on frozen section. Sometimes it can be difficult to discriminate between anaplastic carcinoma and other primary thyroid malignancies (ie, medullary carcinoma, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[95] Metastatic renal carcinoma can mimic follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma.[94] 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).[10,96]

Follicular and Hürthle cell carcinomas are rarely diagnosed by FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.[37,48,62,97] Approximately 15% to 40% of lesions classified as “follicular neoplasm” or “suspicious for follicular neoplasm” are malignant, with risk of malignancy varying by institution, cytopathologist, and whether or not NIFTP is excluded.[98,99] 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.[100] Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful for follicular cell carcinomas (see *FNA Results* in the NCCN Guidelines for Thyroid Carcinoma).[55,86,101]

In some patients with follicular lesions, serum TSH level and thyroid iodine-123 or 99m technetium scanning may identify patients with an autonomously functioning or “hot” nodule who often may be spared surgery, because the diagnosis of follicular adenoma (ie, benign) is highly likely.[3,102] 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 Hürthle cell neoplasm should undergo diagnostic lobectomy or total thyroidectomy, depending on patient preference unless molecular diagnostic testing predicts a low risk of malignancy. In patients with follicular or Hürthle cell neoplasm on FNA who are selected for thyroid surgery in order to obtain a definitive diagnosis, total thyroidectomy is recommended for bilateral disease, unilateral disease greater than 4 cm (especially in men), invasive cancer, metastatic cancer, or if the patient prefers this approach.

When a diagnosis of thyroid carcinoma is promptly established using FNA, the tumor is often confined to the thyroid or has metastasized only to regional nodes; thus, patients can be cured. However, as many as 5% of patients with papillary carcinoma and up to 10% of those patients with follicular or Hürthle cell carcinoma have tumors that aggressively invade structures in the neck or have produced distant metastases. Such cancers are difficult to cure.

Recurrence of Differentiated Thyroid Carcinoma

Depending on initial therapy and other prognostic variables, up to 30% of patients with differentiated thyroid carcinoma may have tumor recurrences during several decades; 66% of these recurrences occur within the first decade after initial therapy.[12] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[103,104] In one large study, central neck recurrences were seen most often in the cervical lymph nodes (74%), followed by the thyroid remnant (20%), and then the trachea or muscle (6%). Of the group with local recurrences, 8% eventually died of cancer.[12] Distant metastases were the sites of recurrence in 21% of patients in this cohort, most often (63%) in the lungs alone. Of the patients with distant metastases, 50% died of cancer.[12]

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.[3,105] These non-palpable, small-volume lymph node recurrences often show little evidence of disease progression over many years and do not appear to be associated with an increase in mortality.[106,107]

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.[12,108-110] Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in men. Thyroid carcinoma is more lethal in patients older than 40 years, increasingly so with each subsequent decade of life. The mortality rate increases dramatically after age 60 years. However, tumor recurrence shows a remarkably different behavior with respect to age. Recurrence frequencies are highest (40%) for those younger than 20 years or older than 60 years; recurrence at other ages ensues in only about 20% of patients.[12,108-111] This disparity between cancer-related mortality and the frequency of tumor recurrence probably accounts for most of the disagreements among clinicians concerning optimal treatment for patients with differentiated thyroid carcinoma. How clinicians assess the importance of tumor recurrence (as opposed to cancer-specific survival) accounts for much of the debate surrounding the influence of age on the treatment plan for children and young adults. A systematic review including five studies showed that risk of tumor enlargement in patients with PTC undergoing active surveillance was negatively associated with age.[112]

Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good.[113,114] 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.[115] 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.[116-118] However, most physicians treating the disease believe that tumor stage and its histologic features should be as significant as the patient's age in determining management.[12,113,119,120] Prognosis is less favorable in men than in women, but the difference is usually small.[12,118] One study found that gender was an independent prognostic variable for survival and that the risk of death from cancer was about twice as high in men as in women.[12] Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.[121]

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 familial adenomatous polyposis,[125] Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands),[126] and Cowden syndrome (multiple hamartomas).[127] The prognosis for patients with all of these syndromes is not different from the prognosis of those with spontaneously occurring papillary carcinoma.

Tumor Variables Affecting Prognosis

Some tumor features have a profound influence on prognosis.[111,128-130] The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, *BRAF* V600E mutation status, and metastases.[74,131,132] For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.[133-136] 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).[96] In patients with sporadic medullary carcinoma, a somatic *RET* oncogene mutation confers an adverse prognosis.[137] A meta-analysis including 13 studies showed that 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.[138] 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.[139] 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 or anaplastic thyroid carcinoma (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 up to 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.[37,140-142]

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.[143,144] NIFTP tumors have a low risk for adverse outcomes and, therefore, require less aggressive treatment.[144-148] 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.[143,144] 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.[149] CAP updated its protocols with NIFTP in the June 2017 version.[96]

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.[68,150-152] However, multiple studies investigating the performance of molecular diagnostics for this subtype have reported that most thyroid nodules histologically diagnosed as NIFTP are classified as “suspicious” by GEC, possibly leading to more aggressive surgical treatment than is necessary.[153,154] Therefore, the validation of molecular diagnostics with NIFTP samples will be necessary to ensure that the tests are accurately classifying these.

Follicular thyroid carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It usually has a microfollicular histologic pattern. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.[155] 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.[156] FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.[48,97] 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).[62] 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.[111] The poor prognosis is closely related to older age at diagnosis, advanced tumor stage, and larger tumor size.[12] 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.[12,157]

When Hürthle (oncocytic) cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as Hürthle cell carcinoma. Previously considered a variant of follicular thyroid carcinoma, the World Health Organization (WHO) and AJCC reclassified Hürthle cell carcinoma as a separate entity in 2017.[10,158] Molecular studies suggest that this tumor may be more similar to papillary than to follicular thyroid carcinomas,[159,160] and genotyping revealed that mutational, transcriptional, and copy number profiles of Hürthle cell carcinomas were distinct from papillary and follicular carcinomas, best categorizing it as a unique class of thyroid malignancy.[161] Benign and malignant Hürthle cell tumors usually cannot be discriminated by FNA or frozen section examination, although large (>4 cm) tumors are more likely to be malignant than smaller ones.[162] Similar to follicular thyroid carcinoma, the diagnosis of Hürthle cell carcinoma is only assigned after analysis of the permanent histologic sections—obtained from diagnostic lobectomy or thyroidectomy—shows tumor capsule invasion by Hürthle cells.

Hürthle cell carcinomas may be aggressive, especially when vascular invasion or large tumors occur in older patients.[163,164] In two large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, about twice the frequency of follicular thyroid carcinoma metastases.[165-167] In contrast to papillary or follicular carcinomas, iodine-131 may be not effective in patients with Hürthle cell carcinoma because fewer Hürthle cell carcinomas concentrate iodine-131. In a series of 100 patients with distant metastases, iodine-131 uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell carcinomas.[165] In the National Cancer Database report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinomas.[168]

Primary Tumor Size

PTCs smaller than 1 cm, termed “incidentalomas” or “microcarcinomas,” are typically found incidentally after surgery for benign thyroid conditions. Their cancer-specific mortality rates are near zero.[169] 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.[170,171] 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,[172] which may be the presenting feature and also may be associated with distant metastases.[169] 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 or larger.[12] In fact, the prognosis for papillary and follicular thyroid carcinomas is incrementally poorer as tumors increase in size.[157,173] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas.[12]

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.[12,174] 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.[12,175]

Lymph Node Metastases

In one review, nodal metastases were found in 36% of 8029 adults with papillary carcinoma, in 17% of 1540 patients with follicular thyroid carcinoma, and in up to 80% of children with papillary carcinoma.[111] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[176] The prognostic importance of regional lymph node metastases is controversial.[3] However, an analysis of more than 9900 patients in the SEER database found a significant difference in survival at 14 years for those with and without lymph node metastases (79% vs. 82%, respectively).[177] Older patients (>45 years) with papillary carcinoma and lymph node metastases also have decreased survival.[178] A 2012 review by Randolph et al emphasized the correlation between the size and number of metastatic lymph nodes and the risk of recurrence.[179] Identification of fewer than 5 sub-cm metastatic lymph nodes was associated with a low risk of recurrence. Conversely, structural disease recurrence rates of more than 20% to 30% were seen in large-volume lymph node metastases (>3 cm, or >5–10 involved lymph nodes).

Distant Metastases

Distant metastases are the principal cause of death from papillary and follicular carcinomas.[180,181] About 50% of these metastases are present at the time of diagnosis.[111] Distant metastases occur even more often in patients with Hürthle cell carcinoma (35%) and in those patients who are older than 40 years at diagnosis.[165,166] 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, site of distant metastasis, and whether the metastases concentrate iodine-131.[165,166,182,183]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[111] However, some pulmonary metastases are compatible with long-term survival.[184] For example, one study found that when distant metastases were confined to the lung, more than 50% of the patients were alive and free of disease at 10 years, whereas no patients with skeletal metastases survived that long.[185] The survival rates are highest in young patients with diffuse lung metastases seen only on iodine-131 imaging and not on x-ray.[183,185,186] Prognosis is worse with large pulmonary metastases that do not concentrate iodine-131.[165,166,182]

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[187] and not the 6th, 7th, or 8th editions.[10,188,189] 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 disease-specific survival, since fewer patients were categorized as stage III and IV under the 8th edition staging.[190]

Prognostic Scoring Strategies

Several staging and clinical prognostic scoring strategies use patient age older than 40 years as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma.[109,116,188,189,191] 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.[173] 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.[116]

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.[119] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[188,192] The AJCC TNM staging approach (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 55 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,[193,194] 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.[109,195]

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.[196-199] 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.[200] This allows ongoing re-assessment of risk and allows the management paradigm to be better tailored to realistic estimates of risk that may change substantially over time.

Surgical Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total Thyroidectomy

The appropriate extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk papillary carcinoma. In most clinical settings, decisions about the extent of thyroidectomy should be individualized and done in consultation with the patient.[201] Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring[118] and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic Cancer Center for low-risk PTCs (MACIS score ≤3.99) had no improvement in survival rates after undergoing procedures more extensive than ipsilateral lobectomy. Thus, the authors concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[202]

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.[203] No significant differences were found in cancer-specific mortality or distant metastasis rates between the two groups. However, the 20-year frequencies of local recurrence and nodal metastasis after unilateral lobectomy were 14% and 19%, respectively, which were significantly higher ($P = .0001$) than the frequencies of 2% and 6% seen after bilateral thyroid lobe resection. Hay et al concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk papillary carcinoma.[203] A more recent 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.[204]

Most NCCN Panel Members recommend total thyroidectomy for patients with biopsy-proven papillary carcinoma who have large-volume pathologic N1 metastases (1 or more nodes 3 cm or larger in largest dimension),[3] because this procedure is associated with improved DFS.[103,120,203,205] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.[111,202] After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and iodine-131 therapy)[12] and the highest frequency (11%) of subsequent pulmonary metastases.[206] However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.[44] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.[12]

However, some prominent thyroid cancer specialists (including some at NCCN Member Institutions) oppose this view and advocate unilateral lobectomy for most patients with papillary and follicular carcinoma based on 1) the low mortality among most patients (ie, those patients categorized as low risk by the AMES and other prognostic classification schemes); and 2) the high complication rates reported with more extensive thyroidectomy.[117,191,207] 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 total lobectomy (without RAI ablation) for patients with papillary carcinoma who have incidental small-volume pathologic N1A metastases (<5 involved nodes with no metastasis >5 mm, in largest dimension).[208]

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 or smaller that is unifocal and confined to the thyroid without vascular invasion (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,209-212] Total lobectomy alone is also adequate treatment for NIFTP pathologies (see *Tumor Variables Affecting Prognosis, Histology*) and minimally invasive follicular thyroid carcinomas (see *Primary Treatment* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). However, completion thyroidectomy is recommended for any of the following: tumor larger than 4 cm in diameter, 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.[131,213,214]

Completion Thyroidectomy

This procedure is recommended when remnant ablation is anticipated or if long-term follow-up is planned with serum Tg determinations and with (or without) whole body iodine-131 imaging. Large thyroid remnants are difficult to ablate with iodine-131.[206] Completion thyroidectomy has a complication rate similar to that of total thyroidectomy. Some experts recommend completion thyroidectomy for routine treatment of tumors 1 cm or larger, because approximately 50% of patients with cancers of this size have additional cancer in the contralateral thyroid lobe.[174,215-221] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[218]

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.[120] 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.[219]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy.[222] Transient clinical hypoparathyroidism postoperatively is common in adults[223] and children[120,224] undergoing total thyroidectomy. The rates of long-term recurrent laryngeal nerve injury and hypoparathyroidism, respectively, were 3% and 2.6% after total thyroidectomy and 1.9% and 0.2% after subtotal thyroidectomy.[225] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[226] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[227] 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.[228]

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 Hürthle Cell Carcinoma). However, a phenomenon termed "stunning" may occur when imaging doses of iodine-131 induce follicular cell damage.[229] Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent iodine-131.[230] 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. Iodine-123 is more expensive, and smaller iodine-131 doses have reduced sensitivity when compared with larger iodine-131 doses.[229-231] 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.[229] 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.[3,229,232,233] 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.[234,235]

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 [RAI]* 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 (RAI)

The NCCN Panel recommends a selective use approach to postoperative RAI administration. The three general, but overlapping, functions of postoperative RAI administration include: 1) ablation of the normal thyroid remnant, which may help in surveillance for recurrent disease (see below); 2) adjuvant therapy to try to eliminate suspected micrometastases; or 3) RAI therapy to treat known persistent disease. The NCCN Guidelines have 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 Hürthle Cell Carcinoma).

Postoperative RAI is typically recommended for patients at high risk of having persistent disease remaining after total thyroidectomy and includes patients with any of the following factors: 1) gross extrathyroidal extension; 2) a primary tumor greater than 4 cm; 3) postoperative unstimulated Tg greater than 10 ng/mL; or 4) 6 or more positive lymph nodes or bulky lymph nodes. In the case of follicular or Hürthle cell 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 Hürthle Cell 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 to 4 cm, high-risk histology (for papillary carcinoma), lymphatic or vascular invasion, cervical lymph node metastases, macroscopic multifocality (one focus >1 cm), unstimulated postoperative serum Tg (<10 ng/mL), or microscopic positive margins.[3,236,237] Tg (even quantitative mass spectrometry approaches) are unreliable for detecting structural disease.[238] Therefore, RAI is also selectively recommended for patients with detectable anti-Tg antibodies. The NCCN Panel does not routinely recommend RAI for patients with all of the following factors: 1) either unifocal (<2 cm) or multifocal classic papillary microcarcinomas (all foci ≤1 cm) confined to the thyroid; 2) no detectable anti-Tg antibodies; and 3) postoperative unstimulated Tg less than 1 ng/mL. 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.[3,239]

Postoperative Administration of RAI

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.[12,110,119,240-242] In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was about 3-fold higher in patients either treated with thyroid hormone alone or given no postoperative medical therapy when compared with patients who underwent postoperative thyroid remnant ablation with iodine-131 ($P < .001$). Moreover, fewer patients developed distant metastases ($P < .002$) after thyroid remnant iodine-131 ablation than after other forms of postoperative treatment. However, this effect is observed only in patients with primary tumors 1.5 cm or larger in diameter.[240] Another study of 21,870 intermediate risk patients with differentiated thyroid cancer found that postoperative RAI improved OS ($P < .001$) and was associated with a 29% reduction in the risk of death after adjustment for demographic and clinical factors (HR, 0.71; 95% CI, 0.62–0.82; $P < .001$).[242] Some studies have found that remnant ablation had less of a therapeutic effect, perhaps because more extensive locoregional surgery had been done.[173]

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.[243] Longer follow-up suggests that OS is not decreased or increased in these patients.[244] 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 RAI.[245] Debate continues about ablating the thyroid bed with iodine-131 after total thyroidectomy.[173,240,246,247] In patients with papillary carcinoma who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates.[212,237,248] A long-term study (n = 1298) found that OS is not improved in patients who receive RAI ablation.[249] Reasons favoring remnant ablation include: 1) simplified patient follow-up, because elimination of thyroid bed uptake prevents misinterpretation of it as disease; 2) elimination of normal tissue as a source of Tg production, which facilitates identification of patients who are free of disease and may simplify their care while promoting early identification of those with residual cancer; and 3) elimination of normal tissue, which may eliminate the nidus for continued confounding anti-Tg antibody production. Conversely, others argue that most recurrences can be easily detected with neck ultrasound and that serum Tg levels are often quite low after a total thyroidectomy.

Therefore, in patients at low and intermediate risk, the clinical benefit of routine remnant ablation as a requirement for optimal follow-up remains uncertain.

Thyroid hormone withdrawal may be recommended to increase uptake from RAI treatment.[250] Duration of time off thyroid hormone depends on the extent of thyroidectomy and approach to hormone replacement in the initial postoperative setting. Two retrospective studies showed that patients with distantly metastatic RAI-avid differentiated thyroid cancer who received recombinant human TSH 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.[251,252] However, thyroid hormone withdrawal continues to be preferred by the NCCN Panel for preparation of RAI treatment compared to thyrotropin alfa, due to an increased likelihood of augmentation of the delivered radiation dose. 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.

Data suggest that lower doses of RAI are as effective as higher doses—30 versus 100 mCi—for ablation in patients with low-risk thyroid cancer (eg, T1b/T2 [1–4 cm], clinical N0 disease).[35,36,253] The NCCN Guidelines reflect a more cautious approach to using RAI ablation based on these randomized trials.[254] If RAI ablation is used, the NCCN Guidelines recommend (category 1) 30 mCi of iodine-131 for RAI ablation in patients at low risk based on these randomized trials. This same ablation dose—30 mCi—may be considered (category 2B) in patients at slightly higher risk.[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.[254] Adverse effects may be minimized by using lower doses of RAI.[35]

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.[3,229,257,258] 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 greater than 30 mCi (1110 MBq). However, hospitalization is no longer necessary in most states, because a change in federal regulations permits the use of much larger iodine-131 doses in patients who are ambulatory.[257] 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 the elderly and in those with impaired kidney function.[259,260] Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of iodine-131 (which is very uncommon) are treated with 150 mCi of iodine-131 (5550 MBq) or less to avoid lung injury, which may occur when more than 80 mCi remains in the whole body 48 hours after treatment. Guidance relating to pediatric patients, women who are breastfeeding or 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 up to 25% of images show lesions that may be clinically important, which were not detected by the diagnostic imaging.[257] 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.[261] Post-treatment imaging was most likely to reveal clinically important new information in patients younger than 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.[261] 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.[262]

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.[263] 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. When initial ablative therapy has been completed, serum Tg should be measured periodically. Serum Tg can be measured while the patient is taking thyroxine, but older studies showed that the test was more sensitive when thyroxine had been stopped or when recombinant human TSH (rhTSH) was given to increase the serum TSH.[264,265] With improved assay sensitivity, Tg stimulated by thyrotropin alfa is no longer more sensitive, and basal Tg on thyroxine can be monitored with accuracy and sensitivity.[266,267]

Using current Tg assays, patients with measurable serum Tg levels during TSH suppression and those with stimulated Tg levels greater than 2 ng/mL are likely to have residual/recurrent disease that may be localized in almost 50% promptly and in an additional 30% over the next 3 to 5 years.[268] About 6% of patients with detectable serum Tg levels (which are <2 ng/mL after stimulation) will have recurrences over the next 3 to 5 years, whereas only about 2% of patients with completely undetectable serum Tg after stimulation will have recurrences over the next 3 to 5 years. The long-term clinical significance is uncertain for disease only detected by minimally elevated Tg levels after stimulation.

Recombinant Human TSH

During follow-up, periodic withdrawal of thyroid hormone therapy has traditionally been used to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements with (or without) 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.[269] Administration of thyrotropin alfa is well tolerated; nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[265] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[269]

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.[265] Data showed that the combination of rhTSH–stimulated whole body imaging and serum Tg measurements detected 100% of metastatic carcinoma.[265] 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 or higher, obtained 72 hours after the last rhTSH injection, indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole body imaging findings.[265,270]

Measuring Serum Tg and Anti-Tg Antibodies

Serum Tg measurement is the best means of detecting thyroid tissue, including carcinoma. Tg can be measured when TSH has been stimulated—either by thyroid hormone withdrawal or by thyrotropin alfa—because in this setting, serum Tg has a lower false-negative rate than whole body iodine-131 imaging.[264,265,268,271] 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. The conditions for TSH–stimulated, whole body iodine-131 imaging stipulate using 4-mCi iodine-131 doses (based on the trial)[265] and an imaging time of 30 minutes or until 140,000 counts are obtained. Tg measurements may also be obtained without stimulating TSH using ultrasensitive assays (ie, second-generation Tg immunometric assays [TgIMAs]).[267,272] Evaluation of serum Tg and anti-Tg antibody levels is helpful for the purpose of obtaining a postoperative baseline.

Functional sensitivity less than or equal to 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.[266,267] 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.[272-274] These antibodies typically falsely lower the Tg value in immunochemiluminometric assays (ICMAs) and immunoradiometric assays (IRMAs), while raising the value in older radioimmunoassays. Although the clinical importance of anti-Tg antibodies is unclear, their persistence for more than 1 year after thyroidectomy and RAI ablation probably indicates the presence of residual thyroid tissue and possibly an increased risk of recurrence.[274]

In one study, 49% of patients had a recurrence if they had undetectable serum Tg and serum anti-Tg antibody levels of 100 units/mL or more when compared with only 3% of patients with undetectable serum Tg and serum anti-Tg antibodies of less than 100 units/mL.[275] In patients with coexistent autoimmune thyroid disease at the time of surgery, anti-Tg antibodies may persist for far longer. In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for up to 20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.[276] Patients with persistently undetectable serum Tg and anti-Tg antibody levels have longer DFS when compared with patients who have detectable levels.[277]

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.[278] 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.[279]

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.[280] 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 papillary, follicular, or Hürthle cell carcinoma, because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium.[246,281-283] 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 below 0.1 mU/L. For patients at low risk and for those patients with an excellent response to initial therapy who are in remission, the recommended TSH level is either slightly below or slightly above the lower limit of the reference range (0.5–2 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 the elderly), bone demineralization (particularly in post-menopausal women), and frank symptoms of thyrotoxicosis.[3,284,285] An adequate daily intake of calcium (1200 mg/day) and vitamin D (1000 units/day) is recommended for patients whose TSH levels are chronically suppressed. 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.[12,240,243,283,288-290] The average dosage needed to attain serum TSH levels in the euthyroid range is higher in patients who have been treated for thyroid carcinoma (2.11 mcg/kg per day) than in those patients with spontaneously occurring primary hypothyroidism (1.62 mcg/kg per day).[290] Even higher doses are required to suppress serum TSH in patients who have been treated for thyroid carcinoma. The optimal TSH level to be achieved is uncertain in patients who have been treated for thyroid carcinoma. Superior outcomes were associated with aggressive thyroid hormone suppression therapy in patients at high risk but were achieved with modest suppression in patients with stage II disease.[243] Excessive TSH suppression (into the undetectable, thyrotoxic range) is not required to prevent disease progression in all patients who have been treated for differentiated thyroid carcinoma.

Adjuvant External-Beam RT

No prospective controlled trials have been completed using adjuvant external-beam radiation therapy (EBRT).[291-293] One retrospective study reported a benefit of adjuvant EBRT after RAI in patients older than 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.[110] 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 patients with 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 RT (IMRT) is safe, effective, and less morbid in patients with thyroid cancer.[296,299,302] There is little evidence regarding appropriate treatment volumes for use of RT for thyroid carcinoma, but 60 to 66 Gy for the postoperative setting (up to 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.[303,304] 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.[305,306] 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.[307] Most recurrent tumors respond well to surgery; iodine-131 therapy; or EBRT, SBRT, or IMRT.[3,308] Local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA) may be considered for select patients with limited burden nodal disease.[3]

Systemic Therapy

Systemic therapy can be considered for tumors that are not surgically resectable; are not responsive to iodine-131; are not amenable to EBRT treatment, SBRT, IMRT, or other local therapies; and have clinically significant structural disease progression during the last 6 to 12 months. 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.[309] Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.[310-317] Agents include multitargeted kinase inhibitors, such as lenvatinib,[310,313,318-325] sorafenib,[326-333] sunitinib,[331,334,335] axitinib,[336-338] everolimus,[339,340] vandetanib,[341] cabozantinib,[311,342] and pazopanib[343]; *BRAF* V600E mutant inhibitors, such as vemurafenib or dabrafenib[344-347]; tropomyosin receptor kinase (TRK) inhibitors, such as larotrectinib or entrectinib[348,349]; *RET* inhibitors such as selpercatinib or pralsetinib[350,351]; and anti-PD-1 antibodies such as pembrolizumab.[352] Data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in patients with papillary carcinoma who have *ALK* gene fusion.[353-356]

Clinical trials suggest that kinase inhibitors have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of subjects, usually for about 12 to 24 months.[313,321,331,343,357-359] 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.[360] 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.[320,321,361-366] Dose modifications of kinase inhibitors may be required. Pazopanib has been reported to cause reversible hypopigmentation.[367]

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.[368] 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.[369] Surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients.[370] In more than 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects.[371] Preoperative ultrasound findings altered the operation in more than 40% of cases. In another report,[372] 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 for locally advanced disease (eg, if the thyroid lesion is fixed, bulky, or substernal) 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 fiber-optic laryngoscopy.[373]

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).[3,374,375] A total thyroidectomy is recommended for patients with any one of the following factors, including: known distant metastases, extrathyroidal extension, tumor larger than 4 cm in diameter, lateral cervical lymph node metastases or gross central neck lymph node metastases, or poorly differentiated histology. Total thyroidectomy may be considered for patients with bilateral nodularity or a prior exposure to radiation (category 2B for radiation exposure). Clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level VI dissection. In the lateral compartment, a formal modified radical neck dissection including levels II, III, IV, and Vb should be performed.[376] Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Based on the results of two randomized controlled trials, the panel does not recommend prophylactic central neck dissection if the cervical lymph nodes are clinically negative. Two trials of randomized patients with cN0 PTC to receive either total thyroidectomy alone or total thyroidectomy plus central neck dissection showed no difference in outcomes between the two groups.[377,378] Central neck dissection will be required ipsilateral to a modified radical neck dissection done for clinically involved lateral neck lymph nodes in most cases. Selective dissection of individual nodal metastases (ie, cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field.

The NCCN Panel did not uniformly agree about the preferred primary surgery for patients with PTC who are assumed to be at lower risk of cancer-specific mortality. As previously mentioned, the extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk PTC, and lobectomy is preferred for these patients, 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.[222] 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 or smaller 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.[379-382]

A study of more than 5000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for patients at low and high risk.[383] An observational study (SEER database) in more than 35,000 patients with PTC limited to the thyroid gland suggests that survival is similar whether (or not) patients are treated in the first year after diagnosis and whether they undergo lobectomy or total thyroidectomy.[384] 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.[243] A study in 52,173 patients found that total thyroidectomy reduces recurrence rates and improves survival in patients with PTC of 1 cm or larger when compared with lobectomy.[385]

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, poorly differentiated disease, or confirmed nodal metastases. While a retrospective study using the National Cancer Database has shown that a sizable percentage of patients with differentiated thyroid cancer receive RAI therapy following lobectomy,[386] 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 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.[387] 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 low or low-normal concentrations can be considered for these patients (see *Principles of TSH Suppression* in the NCCN Guidelines for Thyroid Carcinoma).

Radioactive Iodine Therapy

Postoperative RAI administration is recommended when a number of clinical factors predict a significant risk of recurrence, distant metastases, or disease-specific mortality. Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Algorithms can assist in decision-making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI is not recommended after lobectomy; 3) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 4) RAI is often used for patients with known or suspected distant metastatic disease at presentation. However, some patients may have metastatic disease that may not be amenable to RAI therapy, which is also known as iodine-refractory disease (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Even in the absence of thyroid bed uptake, postoperative RAI treatment may be considered. RAI is also often used to reduce the risk of recurrent thyroid cancer in patients deemed higher-risk based on surgical pathology, even if there is no evidence of structural or biochemical disease present initially in the postoperative period (see *Recurrent Disease* in this Discussion).

All patients should be examined, and cross-sectional imaging (CT or MRI of neck with contrast) should be used to evaluate gross residual disease. Palpable neck disease should be surgically resected before any RAI treatment. A negative pregnancy test is required before the administration of RAI in women of childbearing potential. The administered activity of RAI therapy should be adjusted for pediatric patients.[388] 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 (RAI uptake absent) that is refractory to RAI, EBRT or IMRT 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).[3,299,300,389-391] 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 or IMRT 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 papillary thyroid cancer.[246] In patients treated with lobectomy, disease monitoring following surgery includes physical examination, TSH assessment, and periodic neck ultrasound. If abnormal contralateral nodule or lymph nodes are found, then biopsy should be carried out.

In patients who have had total (or near total) thyroidectomy and thyroid remnant ablation, the ATA Guidelines define the absence of persistent tumor (also known as no evidence of disease [NED]) as: 1) absence of clinical evidence of tumor; 2) absence of imaging evidence of tumor; and 3) undetectable Tg levels (during either TSH suppression or TSH stimulation) and absence of anti-Tg antibodies.[3] Patients treated with total thyroidectomy should be followed with physical examination and measurement of TSH, Tg, and Tg ab. RAI imaging (TSH-stimulated [during either TSH suppression or TSH stimulation]) can be considered in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality; patients with previous RAI-avid metastases; or patients with abnormal Tg levels, stable or increasing Tg ab, or abnormal ultrasound results. A tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 whole body diagnostic imaging done 6 to 12 months after iodine-131 treatment is negative or shows decreasing uptake compared to pretreatment scans.[3] 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]

A subgroup of patients at low risk (eg, micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic neck ultrasound follow-up (without stimulated Tg or follow-up whole body imaging) as long as their basal Tg remains low (see *Disease Monitoring* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Otherwise, long-term ultrasound follow-up is not required. Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.[3] Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.[3]

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

Recurrent Disease

The NCCN Panel agrees that surgery is the preferred therapy for locoregional recurrent disease if the tumor is resectable (see *Recurrent Disease* in the NCCN 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. Preoperative 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 and EBRT or IMRT are recommended if the iodine-131 imaging is positive.[392] Local therapies, such as ethanol ablation or RFA, are also an option if available.[393] EBRT or IMRT alone is another option in the absence of iodine-131 uptake for select patients not responsive to other therapies.[300,394] 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 greater than or equal to 100 mCi of iodine-131 (see *Recurrent Disease* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). The NCCN Panel had a major disagreement (category 3) about recommending post-treatment iodine-131 imaging in this setting, because some do not feel that these patients should have imaging. No study has shown a decrease in morbidity or mortality in patients treated with 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.[395] 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.[396,397] 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).[3,398] Patients should continue to receive levothyroxine to suppress TSH levels. If not already done, then genomic testing should be done to identify potentially actionable mutations (eg, *ALK, NTRK*, 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 EBRT, SBRT, or other local therapies.[303,304,399-401] 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.[402-404] Embolization (or other interventional procedures) of metastases can also be considered either prior to resection or as an alternative to resection.[399,405] RAI is not likely to be curative, but improved survival has been observed in these patients.[184,406]

For solitary or limited CNS lesions, either neurosurgical resection or SRS is preferred (see the NCCN Guidelines for Central Nervous System Cancers).[305,306] For multiple CNS lesions, EBRT 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. If whole brain RT is used, then 30 Gy in 10 daily fractions, or 45 Gy in 1.8 Gy daily fractions if good performance status, are acceptable dosing schedules.[407]

For clinically progressive or symptomatic disease, systemic therapy should be considered. Recommended systemic therapy options include: 1) lenvatinib (preferred) or sorafenib;[320,326] 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.[408,409] Lenvatinib and sorafenib are category 1 options in this setting based on phase 3 randomized trials.[320,326] 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.[318,320,326] 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.[321,410]

Lenvatinib was compared with placebo in patients with metastatic differentiated thyroid cancer that was refractory to RAI in a phase 3 randomized trial.[320] Patients receiving lenvatinib had a progression-free survival (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 in both older (>65 years) and younger (≤65 years) patients. 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 older patients also had higher rates of grade 3 and greater adverse effects from treatment. These results suggest that lenvatinib is an appropriate treatment option for patients of any age with RAI-refractory differentiated thyroid cancer.[411]

Another phase 3 randomized trial compared sorafenib with placebo in patients with RAI-refractory metastatic differentiated thyroid cancer.[326] 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 vascular endothelial growth factor receptor

(VEGFR) TKIs (including lenvatinib and sorafenib).[360] Analyses of the 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. 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 vemurafenib or dabrafenib (for *BRAF*-positive disease), larotrectinib or entrectinib (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,[320,326,362,412,413] and caution should be used in patients with untreated CNS metastases due to the associated bleeding risk.[414] The anti-PD-1 antibody pembrolizumab is also an option for patients with TMB-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) disease.[352] Active surveillance is often appropriate for asymptomatic patients with indolent disease and no brain metastasis.[321,362] 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.[48,415] Unlike PTC, FNA is not specific for follicular thyroid carcinoma and accounts for the main differences in management of the two tumor types.[56,62,97,416] The FNA cytologic diagnosis of "[suspicious for] follicular neoplasm" will prove to be a benign follicular adenoma in 80% of cases. However, 20% of patients with follicular neoplasms on FNA are ultimately diagnosed with follicular thyroid carcinoma when the final pathology is assessed. Molecular diagnostic testing may be useful to determine the status of follicular lesions or lesions of indeterminate significance (including follicular neoplasms, AUS, or FLUS) as more or less likely to be malignant based on the genetic profile.

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 or tumor larger than 4 cm in diameter are apparent at the time of surgery, or if the patient opts for total thyroidectomy to avoid a second procedure (ie, completion thyroidectomy) if cancer is found at pathologic review.[415,417] Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery. 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).

Completion thyroidectomy may also be recommended for tumors that, on final histologic sections after lobectomy plus isthmusectomy, are identified as minimally invasive follicular thyroid carcinomas or encapsulated angioinvasive with less than four vessels. Minimally invasive cancer is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.[3] It is preferred for minimally invasive cancers, as well as NIFTP tumors, to simply be followed carefully, because minimally invasive follicular carcinomas and NIFTP usually have an excellent prognosis. Although deaths attributed to minimally invasive follicular carcinoma do occasionally occur, 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) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

RAI ablation may be used to destroy residual thyroid tissue when RAI uptake is absent; alternatively, these patients may be followed without RAI ablation. Iodine-131 ablation and post-treatment imaging (with consideration of dosimetry for distant metastasis) are recommended for suspected or proven 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 distantly metastatic disease, radioiodine diagnostic imaging (iodine-123 or iodine-131) with adequate TSH stimulation (thyroid withdrawal or thyrotropin alfa) before iodine-131 therapy is administered may be considered, but the problem of stunning should be considered (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).

Hürthle Cell Carcinoma

This tumor (also known as oxyphilic cell carcinoma) is usually assumed to be a variant of follicular thyroid carcinoma,[189,418] although the prognosis of Hürthle cell carcinoma is worse.[164,415,417,419,420] The Hürthle cell variant of PTC is rare and seems to have a prognosis similar to follicular carcinoma.[421] Historically, studies showed that molecular diagnostics did not perform well for Hürthle cell neoplasms.[83,87,88] However, with the advent of newer genomic tests, the validity for Hürthle cell carcinoma is improving (see *FNA Results* in this Discussion, above).[88,89]

The management of Hürthle cell carcinoma is almost identical to follicular thyroid carcinoma, except that 1) locoregional nodal metastases may be more common, and therefore therapeutic lymph node dissections of the affected compartment may be needed for clinically apparent biopsy-proven disease; and 2) metastatic Hürthle cell tumors are less likely to concentrate iodine-131 (see *Papillary Thyroid Carcinoma*: *Surgical Therapy* in this Discussion).[422] Postoperative EBRT or IMRT can be considered for: 1) unresectable primary Hürthle cell lesions 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 Hürthle Cell [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 Hürthle Cell [Thyroid] Carcinoma). The NCCN Guidelines provide algorithms to assist in decision-making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle cell [Thyroid] Carcinoma).

RAI therapy has been reported to decrease the risk of locoregional recurrence and is recommended for unresectable disease with positive iodine-131 imaging. 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 Hürthle Cell [Thyroid] Carcinoma).[164] 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 Hürthle Cell [Thyroid] Carcinoma). Since Hürthle cell carcinoma tends to be non–iodine-avid, negative scans that were done without single-photon emission CT (SPECT) are likely to have missed distant structural disease. Therefore, if Tg is high and/or pathology is high-risk, then FDG-PET is indicated.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid.[423-426] 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.[427,428] Familial MTC is now viewed as a variant of MEN2A.[423,424,429] Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of the disease tend to present at earlier ages.[423,424] The 5-year relative survival for stages I to III is about 93%, whereas 5-year survival for stage IV is about 28%.[168,189] 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.[430] Distant metastases in the lungs or bones cause symptoms in 5% to 10% of patients. Many patients with advanced MTC can have diarrhea, Cushing syndrome, or facial flushing, because the tumor can secrete calcitonin and sometimes other hormonally active peptides (ie, adrenocorticotropic hormone [ACTH], calcitonin gene-related peptide [CGRP]). Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms.[431] Patients with unresectable or metastatic disease may have either slowly progressive or rapidly progressive disease.

Nodule Evaluation and Diagnosis

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

Sporadic MTC

Sporadic MTC is usually suspected after FNA of a solitary nodule (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). Reports suggest that about 3% of patients with nodular thyroid disease will have an increased serum calcitonin level when measured by a sensitive immunometric assay; 40% of these patients will have MTC at thyroidectomy.[432-434] 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.[435,436] The ATA is equivocal about routine calcitonin measurement.[3]

Inherited MTC

For patients with known kindreds with inherited MTC, prospective family screening with testing for mutant *RET* genes can identify disease carriers long before clinical symptoms or signs are noted.[425,426] The traditional approach of stimulating secretion of calcitonin by either pentagastrin or calcium infusion to identify patients with MTC is no longer recommended, because elevated calcitonin is not a specific or adequately sensitive marker for MTC[437] and because pentagastrin is no longer available in the United States. When MEN2A is suspected, the NCCN Guidelines recommend measurement of calcium levels with (or without) serum intact parathyroid hormone levels (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade of life, without gender preference. In patients with MEN2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.

All familial forms of MTC and MEN2 are inherited in an autosomal-dominant fashion. Mutations in the *RET* proto-oncogene are found in at least 95% of kindreds with MEN2A and 88% of cases of familial MTC.[425,426,438] The *RET* proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; MEN2B and some familial MTC mutations are found within the intracellular exons 14 to 16.[423,424] Somatic mutations in exons 11, 13, and 16 have also been found in at least 25% of sporadic MTC tumors—particularly the codon 918 mutation that activates the tyrosine kinase function of the receptor—and are associated with poorer prognosis of the patient.

About 6% of patients with clinically sporadic MTC carry a germline *RET* mutation, leading to identification of new kindreds with multiple (previously undiagnosed) affected individuals.[439,440] Germline testing for *RET* proto-oncogene mutations with genetic counseling by a physician or genetic counselor is recommended for all patients with newly diagnosed, clinically apparent, sporadic MTC.[441] 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.[442] 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 carcinoembryonic antigen [CEA]) and screening of patients with germline *RET* proto-oncogene mutations for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A). Before surgery for MTC, it is important to diagnose and address coexisting pheochromocytoma to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org). Pheochromocytoma can be removed using laparoscopic adrenalectomy.[423,424,443] 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, such as in cases of high burden of disease, calcitonin greater than 400 pg/mL, or elevated CEA levels. Distant metastasis does not contraindicate surgery.[423,424] Liver imaging is rarely needed if calcitonin is less than 400 pg/mL. Evaluation of vocal cord mobility can also be considered for patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.

Staging

As previously mentioned, the NCCN Guidelines for Thyroid Carcinoma do not use TNM stages to guide therapy. Instead, many characteristics of the tumor and patient play important roles in these NCCN Guidelines. Many specialists in thyroid cancer also follow this paradigm. The TNM criteria for clinicopathologic tumor staging are based on tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma).[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[187] and not to the 6th, 7th, or 8th editions.[10,188,189]

However, the TNM staging classification lacks other important prognostic factors.[444] Notably absent is the age at diagnosis. Patients younger than 40 years at diagnosis have a 5- and 10-year disease-specific survival rate of about 95% and 75%, respectively, compared with 65% and 50% for those older than 40 years.[430,444] 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.[445,446] 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.[446]

Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor[447]; 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level[448]; and 3) postoperative residual hypercalcitoninemia.[449] 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.[444,450] Codon analysis is useful for predicting prognosis.[423,424,451] Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN2B, is associated with more aggressive disease.[452] 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).[453]

Surgical Management

Surgery is the main treatment for MTC. While no curative systemic therapy for MTC is available, vandetanib and cabozantinib are recommended for locally advanced and metastatic MTC (see *Recurrent or Persistent Disease* in this Discussion).[454-457] MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, iodine-131 imaging cannot be used, and RAI treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, TSH suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levothyroxine dose.[423,424]

Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease, because the possibility of MEN2 should dictate testing for a germline *RET* proto-oncogene mutation for all patients with MTC. Pheochromocytomas should be removed (eg, laparoscopic adrenalectomy) before surgery on the thyroid to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org).

Patients with pheochromocytomas must be treated preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery. Forced hydration and alpha-blockade are necessary to prevent hypotension after the tumor is removed. After institution of alpha-blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is 1 cm or larger or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is smaller than 1 cm and for unilateral thyroid disease (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[374,430] Given the risks of thyroidectomy in very young children, referral to a surgeon and team with experience in pediatric thyroid surgery is advised.

If a patient with inherited disease is diagnosed early enough, the recommendation is to perform a prophylactic total thyroidectomy by age 5 years or when the mutation is identified (in older patients), especially in patients with codon 609, 611, 618, 620, 630, or 634 *RET* mutations.[423,424,458] Note that C634 mutations are the most common mutations.[423,424] Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN2B who have codon 883 *RET* mutations, 918 *RET* mutations, or compound heterozygous (V804M + E805K, V804M + Y806C, or V804M + S904C) *RET* mutations (see *Clinical Presentation* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma), because these *RET* mutations carry the highest risk for MTC (ie, level D).[423,424,459]

However, for patients with codon 768, 790, 791, 804, and 891 *RET* (risk level A) mutations, the lethality of MTC may be lower than with other *RET* mutations.[423,424,459,460] In patients with these less high-risk (ie, lower-risk level A) *RET* mutations, annual basal calcitonin testing and annual ultrasound are recommended; total thyroidectomy and central node dissection may be deferred if these tests are normal, there is no family history of aggressive MTC, and the family agrees to defer surgery (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[423,424,461,462] Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.[423,424,460,461,463] A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with RET mutations for MEN2A; longer follow-up is necessary to determine if these patients are cured.[464]

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.[423,424] A bilateral central neck dissection (level VI) can be considered for all patients with MEN2B. For those patients with MEN2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if patients have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for these patients with primary tumor(s) 1 cm or larger in diameter (>0.5 cm for patients with MEN2B) or for patients with central compartment lymph node metastases (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

With a concurrent diagnosis of hyperparathyroidism in MEN2A or familial MTC, the surgeon should leave or autotransplant the equivalent mass of one normal parathyroid gland if multiglandular hyperplasia is present. Cryopreservation of resected parathyroid tissue should be considered to allow future implantation in the event of iatrogenic hypoparathyroidism. Disfiguring radical node dissections do not improve prognosis and are not indicated. In the presence of grossly invasive disease, more extended procedures with resection of involved neck structures may be appropriate. Function-preserving approaches are preferred. In some patients, MTC is diagnosed after thyroid surgery. In these patients, additional workup is recommended to ascertain whether they have RET proto-oncogene mutations (eg, exons 10, 11, 13–16), which will determine whether they need additional surgery (eg, completion thyroidectomy and/or neck dissection) (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

Adjuvant RT

EBRT and IMRT have not been adequately studied as adjuvant therapy in MTC.[301,423,465] Slight improvements in local DFS have been reported after EBRT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement.[466] However, most centers do not have extensive experience with adjuvant EBRT or IMRT for this disease. While therapeutic EBRT or IMRT may be considered for grossly incomplete resection when additional attempts at surgical resection have been ruled out, adjuvant EBRT or IMRT is rarely recommended (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[423,424] EBRT or IMRT can also be given to palliate painful or progressing bone metastases.[303,304,401,423,424] There is little evidence regarding appropriate treatment volumes for use of RT for MTC, but 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 greater than 1000 pg/mL—and with no obvious MTC in the neck and upper mediastinum—probably have distant metastases, most likely in the liver. However, occasionally patients have relatively low serum CEA and calcitonin levels but have extensive metastatic disease; initial postoperative imaging is therefore reasonable despite the absence of very high serum markers.

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease, 15 patients with MEN2A, and 6 patients with MEN2B), the 5- and 10-year survival rates were 90% and 86%, respectively.[467] Two studies have reported higher mortality rates for patients with high postoperative serum calcitonin values, with more than 50% of patients having a recurrence during a mean follow-up of 10 years.[449,468] Routine lymphadenectomy or excision of palpable tumor generally fails to normalize the serum calcitonin concentrations in such patients; therefore, some have focused on detection and eradication of microscopic tumor deposits with a curative intent in patients without distant metastases. Extensive dissection to remove all nodal and perinodal tissue from the neck and upper mediastinum was first reported to normalize the serum calcitonin levels in 4 of 11 patients at least 2 years postoperatively.[469] 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.[470,471] 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.[471]

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 MEN2, annual screening for pheochromocytoma (MEN2B or MEN2A) and hyperparathyroidism (MEN2A) should also be performed. For some low-risk *RET* mutations (eg, codons 768, 790, 804, or 891), less frequent screening may be appropriate.

Patients with detectable serum markers (ie, calcitonin levels ≥150 pg/mL) should have CT or MRI of the neck, chest, and liver. Bone scan and MRI of axial skeleton should be considered in select patients such as those with very elevated calcitonin levels.[423,424] 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.[423,424]

For patients with asymptomatic disease and detectable markers in whom imaging fails to identify foci of disease, the NCCN Panel recommends conservative surveillance with repeat measurement of the serum markers every 6 to 12 months. 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.[321,472,473] Vandetanib and cabozantinib are oral receptor kinase inhibitors that increase PFS in patients with metastatic MTC.[454,457,474-476] *RET* inhibitors that are FDA-approved for *RET*-mutated MTC include selpercatinib and pralsetinib.[350,351]

Vandetanib is a multitargeted kinase inhibitor; it inhibits RET, VEGFR, and endothelial growth factor receptor (EGFR).[454] In a phase III randomized trial in patients with unresectable, locally advanced, or metastatic MTC (n = 331), vandetanib increased PFS when compared with placebo (HR, 0.46; 95% CI, 0.31–0.69; *P* < .001); OS data are not yet available.[454] A post-hoc subgroup analysis including 184 patients with symptomatic and progressive disease at baseline also showed increased PFS (HR, 0.43; 95% CI, 0.28–0.64; *P* < .001) in patients who received vandetanib, compared to the 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).[477] In this subgroup, the overall response rate (ORR) was

37% in the patients who received vandetanib and 2% in patients who received the 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.[455] However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity.[478] 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 increased median PFS when compared with placebo (11.2 vs. 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; *P* < .001).[457] Following long-term follow-up, 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, .64–1.12, *P* = .24).[479] 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.[479,480] In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC.[456] The NCCN Panel 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,[481,482] supporting investigation into the impact of recently developed *RET* inhibitors on *RET*-mutated MTC. The phase I–II LIBRETTO-001 study evaluated the efficacy of the *RET* inhibitor selpercatinib in 143 patients with *RET*-mutant MTC.[350] In patients previously treated with vandetanib or cabozantinib (n = 55), the ORR and 1-year PFS rates were 69% (95% CI, 55%–81%) and 82% (95% CI, 69%–90%), respectively. In patients with no previous vandetanib or cabozantinib treatment (n = 88), the ORR and 1-year PFS rates were 73% (95% CI, 62%–82%) and 92% (95% CI, 82%–97%), respectively. The most commonly reported toxicities (grade 3 and 4) were hypertension (21%), increased alanine aminotransferase (11%), increased aspartate aminotransferase (9%), hyponatremia (8%), and diarrhea (6%). Dose reductions due to treatment-related adverse events were reported in 30% of patients. Pralsetinib, another *RET* inhibitor, was evaluated in the phase I–II ARROW study, which included 92 patients with *RET*-mutant MTC.[483] The ORR was 60% (95% CI, 46%–74%) in patients previously treated with vandetanib 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. Based on the data and the FDA approvals, the NCCN Panel recommends selpercatinib and pralsetinib as preferred options for patients with *RET*-mutant disease (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). *RET* somatic genotyping may 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 with (or without) postoperative EBRT or IMRT. For unresectable locoregional disease that is symptomatic or progressing by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[484] the following options can be considered: 1) RT (EBRT or IMRT); or 2) systemic therapy. Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include: 1) palliative resection, ablation (eg, radiofrequency, embolization), or other regional treatment; 2) vandetanib (category 1); or 3) cabozantinib (category 1) (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but 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 or pralsetinib 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.[352] The NCCN Panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone.

In the setting of symptomatic disease or progression, the NCCN Panel recommends 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 or pralsetinib 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.[334,485-490] If the patient progresses on a preferred option, then systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.[423,491-493] Pembrolizumab is also an option for patients with TMB-H (≥10 mut/Mb) disease (useful in certain circumstances).[352] EBRT or IMRT can be used for local symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.[402-404] Best supportive care is also recommended.

Results from clinical trials have shown the effectiveness of novel multitargeted therapies including sunitinib,[334,335] sorafenib,[412,486] lenvatinib,[489] and pazopanib[488] in MTC. Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.[362,365,408,413] Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.[362]

Novel therapies and the management of aggressive MTC have been reviewed.[315,423,494-497] 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.[498] A phase 2 trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with iodine-131.[499] OS was improved in the subset of patients with increased calcitonin doubling times.[500]

Anaplastic Thyroid Carcinoma

ATCs are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[501] Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[502] Fewer than 10% of patients are younger than 50 years, and 60% to 70% of patients are women.[108,502] The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.[501,503] 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.[31]

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.[504] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Iodine deficiency is associated with ATC. More than 80% of patients with ATC have a history of goiter.[503,505,506] Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, iodine-131 imaging cannot be used.

ATC is typically diagnosed based on clinical symptoms, unlike differentiated thyroid carcinoma, which is typically diagnosed after FNA on a suspicious thyroid nodule. Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner syndrome, stroke, and hoarseness due to vocal cord paralysis.[507] Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[508,509] 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 diagnosis of ATC is usually established by core or surgical biopsy. If FNA is suspicious or not definitive, core or surgical biopsy should be performed to establish the diagnosis of ATC.[510] 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.[95,510]

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.[507] 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.[511] 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 usually 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*). [510]

Prognosis

No curative therapy exists for ATC; it is almost uniformly fatal.[512,513] The median survival from diagnosis is about 5 months.[503,514] The 1-year survival rate is about 20%.[509,514] 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.[515] 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.[516] Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, white blood cell (WBC) count greater than or equal to 10,000 mm^3, and dyspnea as a presenting symptom.[517,518] 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.[519] 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.[510] The role of palliative and supportive care is paramount and should be initiated early in the disease.[510] At the outset of the diagnosis, it is critical that conversations about end-of-life care be initiated so that a clear understanding of how to manage the airway is undertaken, which is clear to the family and all providers. Tracheostomy is often a morbid and temporary treatment of the airway and may not be the option a patient would choose.[515,520]

Surgery

Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.[501] Before resection is attempted, the extent of disease—particularly in the larynx, trachea, and neck—should be accurately assessed by a very experienced surgeon who is capable of performing extensive neck dissections, if necessary. However, most patients with ATC have unresectable or metastatic disease. The patency of the airway should be assessed throughout the patient's course of treatment.[515] If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with selective resection of all involved local or regional structures and nodes.[510] 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.[514,516,521,522] Patients need to receive levothyroxine if total thyroidectomy is done. Tracheostomy may be considered in patients with stage IVc disease.

Radiation Therapy

EBRT or IMRT can increase short-term survival in some patients; EBRT or IMRT can also improve local control and can be used for palliation (eg, to prevent asphyxiation).[465,501,510,518,523-527] Adjuvant RT, especially when combined with concurrent chemotherapy, is associated with improved survival.[528] Higher RT dose is associated with OS in patients with unresected ATC.[529] Surgical excision or external irradiation should be considered for isolated skeletal metastases. 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 should commence as quickly as possible. For R0 or R1 resection, adjuvant RT should begin as soon as the patient has sufficiently recovered from surgery, ideally 2 to 3 weeks postoperatively. 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,[530] larotrectinib or entrectinib are options for *NTRK* gene fusion-positive tumors,[348,349,531] selpercatinib or pralsetinib are options for *RET* fusion-positive disease,[350,351] and pembrolizumab is an option for TMB-H (≥10 mut/Mb) disease.[352] Other recommended regimens include paclitaxel and doxorubicin monotherapies.[510] Doxorubicin combined with cisplatin is an option based on a small randomized trial.[532] 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[510] and less panel consensus.

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.[510]

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.[530] The confirmed ORR was 69% (95% CI, 41%–89%), with seven responses ongoing. While duration of response, PFS, and OS were not yet reached, the 12-month estimates were 90%, 79%, and 80%, respectively. The combination was found to be well-tolerated as evaluated in 100 patients across seven rare tumor types; common adverse events included fatigue (38%), pyrexia (37%), and nausea (35%).[530] Based on these data, the FDA approved dabrafenib/trametinib for ATC with *BRAF* V600E mutation in 2018.

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.[348,533] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment.[348,533] One hundred percent of the thyroid cancers in this study responded to larotrectinib, with one complete response and four partial responses.[533] 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.[348] 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.[349] Based on these data, the FDA approved larotrectinib and entrectinib for treatment of patients with *NTRK* gene fusion-positive tumors, and the panel also recommends *NTRK* therapy options such as larotrectinib or entrectinib 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% DCR).[351] In 2020, the FDA approved both of these *RET* inhibitors for RAI-refractory *RET* fusion-positive thyroid cancer requiring systemic therapy.

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.[352] 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.[534] The ORR was only 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 greater than 50% (35%; 95% CI, 14.2%–61.7%).

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.[510,527] 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.[532] 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.[535-537] If weekly paclitaxel is used, the ATA Guidelines[510] 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.[537]

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.[335,538-546] 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).[538,547] Preliminary data suggest that ALK inhibitors may be effective in a subset of patients with papillary thyroid cancer who have ALK gene fusions; however, these ALK gene fusions are rarely reported in patients with ATC.[353-356]

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.[548] Distant metastases then become the leading cause of death.[549] 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.[527,550-552] IMRT may be useful to reduce toxicity.[465,510,553-557] 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.[535,537,554,558] 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.[559]

Multimodality therapy is recommended in patients with locally resectable disease (see *Treatment* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[510,538,553,560-564] 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.[565,566] In a case series, complete surgical resection without tracheostomy or radical re-resection was achieved in six patients with initially unresectable *BRAF* V600E-mutated anaplastic thyroid carcinoma who received neoadjuvant dabrafenib/trametinib.[567] 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.

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