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## Thyroid Carcinoma

**NCCN Thyroid Carcinoma Panel Members**

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Updates in Version 2.2017 of the NCCN Guidelines for Thyroid Carcinoma from Version 1.2017 include:

THYR-1
Clinical Presentation
- 2nd bullet was revised: “Ultrasound of thyroid and central neck”
- 3rd bullet was removed: “Ultrasound of lateral neck (category 2B)”
- Workup statement referring to “Thyroid nodule(s) with low TSH” was revised: “Radioiodine imaging thyroid uptake and scan”

THYR-2
Sonographic Features
- Paragraph was revised: “The above criteria serve as general guidelines. In patients with high-risk clinical features, evaluations of nodules smaller than listed may be appropriate depending on clinical concern. Allowance for informed patient desires would include excisional biopsy (lobectomy or thyroidectomy) for definitive histology, especially in larger nodules (>4 cm) or higher risk clinical situations.”
- Footnote “g” was added: “Suspicious lymph node features may include hypoechoic, rounded, absence of fatty hilum, cystic or partially cystic, and/or microcalcifications.”
- A footnote was removed: “High-risk clinical features: radiation exposure as child or adolescent; first-degree relative with thyroid cancer or MEN2; FDG avid on PET scan; personal history of thyroid cancer-associated conditions such as familial adenomatous polyposis, Carney complex, or Cowden syndrome; personal history of thyroid cancer in lobectomy.”

THYR-3
- “Follicular or Hürthle cell neoplasm,” and “Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS)”
- 2nd bullets were revised: “Consider molecular diagnostics for follicular cell neoplasm (1st bullet only) may be employed (category 2B)”
- Footnote “l” was added: “Total thyroidectomy may be considered for Hürthle cell, history of radiation exposure, or contralateral lobe lesions.”
- Footnote “m” was added: “Molecular diagnostics are not recommended for Hürthle cell neoplasm.” (Also for THYR-4)

THYR-4
- This page was reformatted.
- FNA results
- Statement was revised: “Consider molecular diagnostics may be employed (category 2B 2A)”
- Footnote “o” was added: “Clinical risk factors, sonographic patterns, and patient preference can help determine whether observation or lobectomy is appropriate.”
Papillary Carcinoma

PAP-1

• Diagnostic Procedures
  3rd bullet was revised: “Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)” (Also for FOLL-1, HÜRT-1, MEDU-1, and ANAP-1)
  4th bullet was revised: “Consider FNA for suspicious lateral neck nodes in lateral neck should be further evaluated by ultrasound-guided FNA for staging and guiding extent of surgery”
  A footnote was added: "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." (Also for FOLL-1, HÜRT-1, MEDU-1, and ANAP-1)

• Preoperative or Intraoperative Decision-Making Criteria
  5th bullet under, “Indications for total thyroidectomy or lobectomy, if all criteria present” was revised: “Tumor ≤ 4 cm in diameter”

• Primary Treatment
  1st statement was revised: “Total thyroidectomy Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease Consider prophylactic central neck dissection (level VI) (category 2B)

Lobectomy + isthmusectomy (category 2B)
  ◊ 3rd bullet was added under “All of the following”: “NIFTP pathologic diagnosis” (Also for FOLL-1 and HÜRT-1)
  ◊ A footnote was added: “RAI not recommended after lobectomy.” (Also for FOLL-1 and HÜRT-1)
  ◊ A footnote was added: “Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), has been reclassified and only lobectomy is needed.” (Also for PAP-2, FOLL-1 and HÜRT-1)

• Footnote “b” was revised: “Use of iodinated contrast will delay treatment with RAI but is required for optimal cervical imaging using CT, although iodinated contrast will delay treatment with RAI.” (Also for FOLL-1 and HÜRT-1)

Papillary Carcinoma continued

PAP-1

• Footnote “d” was revised: “Completion thyroidectomy is not required for small volume pathologic N1A micrometastases (≤ 5 involved nodes with no micrometastasis, > 2 mm 0.5 cm in largest dimension). See (PAP-4).” (Also for PAP-2)
  • A footnote was removed: "Possible benefit to reduce recurrence for patients with T3-T4 lateral disease must be balanced with risk of hypoparathyroidism and recurrent laryngeal nerve damage."

PAP-4

• “RAI not typically recommended (if all present)”
  ◊ 2nd bullet was revised: “< 2 cm” (Also for HÜRT-3)
  ◊ “RAI selectively recommended (if any present)”
  ◊ 1st bullet was revised: “Primary tumor ≤ 2–4 cm” (Also for HÜRT-3)

PAP-5

• Original PAP-5 page was removed.
  • Statement was revised: “Consider pretreatment 123I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH); (category 2B)” (Also for FOLL-5 and HÜRT-5)
  • "Suspected or proven thyroid bed uptake" statement was revised: "Follow without RAI ablation or Selective use of RAI for remnant ablation (30–50 mCi) adjuvant therapy (50–100 mCi) post-treatment imaging (whole body RAI scan)" (Also for PAP-6, FOLL-5, FOLL-6, and HÜRT-5)
  • Suspected or proven radiiodine avid metastatic foci
  ◊ Statement was revised: “RAI therapy (100–200 mCi); post-treatment imaging (whole body RAI scan)” (Also for PAP-6, FOLL-5, FOLL-6, HÜRT-5, and HÜRT-6)
  ◊ Footnote “q” was added to statement: "The administered activity of RAI therapy should be adjusted for pediatric patients."
Papillary Carcinoma continued

PAP-7
- Long-term surveillance statement was revised: "Patients treated with $^{131}$I ablation, with a negative ultrasound, stimulated Tg < 2 ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulated thyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging (CT or MRI with contrast or bone scan or chest x-ray) as clinically appropriate, may be considered if clinical suggestion of recurrent disease." (Also for FOLL-7 and HÜRT-7)

PAP-8
- "Locoregional recurrence” statement was revised: “Surgery (preferred) if resectable and/or Radioiodine treatment, if radioiodine imaging positive and/or EBRT/IMRT, if radioiodine imaging negative and/or local therapies when available (ethanol ablation, RFA) and/or EBRT/IMRT, if radioiodine imaging negative for select patients not responsive to other therapies, or observation for low-volume disease that is stable and distant from critical structures” (Also for FOLL-8 and HÜRT-8)

PAP-9
- 4th bullet for "iodine-refractory unresectable loco-regional recurrent/persistent disease" and "iodine-refractory soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)" was revised: “Active surveillance may be is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis." (Also for FOLL-9 and HÜRT-9)
- A footnote was revised: "While not FDA approved for treatment of differentiated thyroid cancer, commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, er vandetanib, vemurafenib [BRAF-positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate. (Also for PAP-10, FOLL-9, FOLL-10, HÜRT-9 and HÜRT-10)

Follicular Carcinoma

FOLL-9
- 4th bullet for "iodine-refractory unresectable loco-regional recurrent/persistent disease" and "iodine-refractory soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)" was revised: "Active surveillance may be is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis. [See FOLL-7]"

FOLL-10
- For "CNS Metastases" a bullet was removed: "Active surveillance may be appropriate in asymptomatic patients with indolent disease. (see FOLL-7)" (Also for HURT-10)

Medullary Carcinoma

MEDU-1
- Primary Treatment
  ‣ A bullet was revised: “Consider Adjuvant EBRT/IMRT is for gross residual disease rarely recommended)” (Also for MEDU-3, MEDU-4)

MEDU-2
- Additional Workup
  ‣ 3rd bullet was revised: "Screen for germline RET proto-oncogene mutations"
  ‣ Statement revised: "Germline RET positive mutation identified"
  ‣ Statement revised: "Germline RET negative mutation not identified"

MEDU-3
- Primary Treatment
  ‣ 4th bullet was revised: "Consider Adjuvant EBRT/IMRT for gross residual disease is rarely recommended" (Also for MEDU-4)
Medullary Carcinoma continued

MEDU-5

- Detectable basal calcitonin or elevated CEA
  - 1st bullet was revised: "Neck ultrasound imaging"
  - 2nd bullet was revised: "If calcitonin \( \geq 150 \, \text{pg/mL} \), cross-sectional imaging should include contrast-enhanced CT (\( \pm \) PET) or MRI of the neck, chest, abdomen with liver protocol"
  - 3rd bullet was added: "Bone scan in select patients"

MEDU-6

- Treatment for locoregional disease
  - 3rd statement was revised: "Consider vandetanib (category 1) or cabozantinib (category 1) for unresectable disease that is symptomatic or structurally progressing by RECIST criteria"
    (Also for MEDU-7)
  - 4th statement was revised: "Observe Active surveillance"
  - Footnote "r" was added: "Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone." (Also for MEDU-7)

MEDU-7

- Symptomatic disease or progression
  - 2nd bullet was revised: "EBRT/IMRT for focal local symptoms (Also for ANAP-2)
  - Footnote "t" was revised: "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, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib"

Anaplastic Carcinoma

ANAP-1

- Diagnostic Procedures
  - 7th bullet was revised: "\( ^{18} \text{FDG PET/CT (skull base to mid-thigh)} \)"
  - 9th bullet was added: "Direct exam of larynx"
Clinical Trial: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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

**CLINICAL PRESENTATION**

For thyroid nodule known or suspected on exam or incidental imaging finding:
- Measure thyroid-stimulating hormone (TSH)
- Ultrasound of thyroid and neck

**WORKUP**

- **Thyroid nodule(s) with low TSH**
  - Radioiodine imaging thyroid uptake and scan
  - Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)\(^b\)

- **Thyroid nodule(s) with normal or elevated TSH**\(^a\)
  - Autonomous functioning (hot)
  - Hypofunctional
  - Consider fine-needle aspiration (FNA) or ultrasound-guided FNA based on clinical and sonographic features

\(^a\) Evaluate and treat for hypothyroidism as clinically indicated.

\(^b\) For nodules not meeting criteria for FNA, or nodules that appear to be benign by ultrasound or FNA, surveillance should include repeat ultrasound after 6–12 months; if stable for 1–2 years, then subsequent ultrasound can be considered at 3- to 5-year intervals.
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## Thyroid Carcinoma – Nodule Evaluation

### SONOGRAPHIC FEATURES

<table>
<thead>
<tr>
<th>Condition</th>
<th>Threshold for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid nodule&lt;br&gt;• With suspicious sonographic features&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥1.0 cm</td>
</tr>
<tr>
<td>Solid nodule&lt;br&gt;• Without suspicious sonographic features</td>
<td>≥1.5 cm</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule&lt;br&gt;• With suspicious sonographic features&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Solid component &gt;1 cm</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule&lt;br&gt;• Without suspicious sonographic features</td>
<td>Solid component &gt;1.5 cm</td>
</tr>
<tr>
<td>Spongiform nodule&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≥2.0 cm</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>Not indicated&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Suspicious cervical lymph node&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>FNA node ± FNA-associated thyroid nodule(s)</td>
</tr>
</tbody>
</table>

The above criteria serve as general guidelines. Allowance for informed patient desires would include lobectomy or thyroidectomy for definitive histology, especially in larger nodules (>4 cm) or higher risk clinical situations.

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<sup>b</sup>For nodules not meeting criteria for FNA, or nodules that appear to be benign by ultrasound or FNA, surveillance should include repeat ultrasound after 6–12 months; if stable for 1–2 years, then subsequent ultrasound can be considered at 3- to 5-year intervals.

<sup>c</sup>Suspicious sonographic features include hypoechoic, microcalcifications, infiltrative margins, and taller than wide in the transverse plane. Sonographic features associated with a low risk of malignancy include spongiform nodules, isoechoic or hyperechoic solid nodules, and mixed solid-cystic nodules without any of the suspicious features listed above.

<sup>d</sup>Aggregation of multiple microcystic components in more than 50% of the volume of the nodule.

<sup>e</sup>Except as therapeutic modality.

<sup>f</sup>Tg washout may be helpful in diagnosis of lymph node metastases.

<sup>g</sup>Suspicious lymph node features may include hypoechoic, rounded, absence of fatty hilum, cystic or partially cystic, and/or microcalcifications.

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## Thyroid Carcinoma – Nodule Evaluation

### FNA RESULTS

<table>
<thead>
<tr>
<th>Carcinoma or suspicious for carcinoma</th>
<th>Papillary or suspicious for papillary</th>
<th>See Primary Treatment (PAP-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary or suspicious for medullary</td>
<td>See Primary Treatment (MEDU-1)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic or suspicious for anaplastic</td>
<td>See Primary Treatment (ANAP-1)</td>
<td></td>
</tr>
</tbody>
</table>

### Follicular or Hürthle cell neoplasm

<table>
<thead>
<tr>
<th>Atypia of undetermined significance/ Follicular lesion of undetermined significance (AUS/FLUS)</th>
<th>High clinical and/or radiographic suspicion of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Consider lobectomy or total thyroidectomy(^{1}) for definitive diagnosis/treatment</td>
</tr>
<tr>
<td>No</td>
<td>• Consider diagnostic lobectomy</td>
</tr>
<tr>
<td></td>
<td>• Consider molecular diagnostics for follicular cell neoplasm (^{1, m})</td>
</tr>
<tr>
<td></td>
<td>• Consider observation if low risk or patient preference</td>
</tr>
</tbody>
</table>

### Treatment Pathways

- **Yes**
  - Consider diagnostic lobectomy
  - Consider molecular diagnostics for follicular cell neoplasm
  - Consider observation if low risk or patient preference

- **No**
  - Consider lobectomy or total thyroidectomy\(^{1}\) for definitive diagnosis/treatment
  - • Consider diagnostic lobectomy
  - • Consider molecular diagnostics\(^{1}\)
  - • Repeat FNA\(^{n}\)
  - • Observe

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\(^{1}\)Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 20%–30%.

\(^{1}\)The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA.

Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (FLUS)) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see (PAP-1). If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.

\(^{1}\)Alternative terms include: rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%–10%.

\(^{n}\)Based on rapid growth of nodule, imaging, physical exam, age, clinical history of radiation, and family history.

\(^{1}\)Total thyroidectomy may be considered for Hürthle cell, history of radiation exposure, or contralateral lobe lesions.

\(^{m}\)Molecular diagnostics are not recommended for Hürthle cell neoplasm.

\(^{1}\)Consider second opinion pathology.

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Thyroid Carcinoma – Nodule Evaluation

FNA RESULTS

AUS/FLUS\(^{ij}\)  
Consider molecular diagnostics\(^i\)

Molecular diagnostics  
- Not done  
- Not informative  

Observe or  
Consider lobectomy for definitive diagnosis/treatment\(^o\)

Molecular diagnostics indicate benign lesion\(^i\)

Consider lobectomy or total thyroidectomy for definitive diagnosis/treatment

Molecular diagnostics suggestive of malignancy  

Observe or  
consider lobectomy for definitive diagnosis/treatment\(^i,o\)

Follicular neoplasm\(^{h,i}\)  
Consider molecular diagnostics\(^i,m\)

Molecular diagnostics  
- Not done  
- Not informative  

Molecular diagnostics indicate benign lesion\(^i\)


\(^{h}\)Alternative term: Suspicious for follicular neoplasm. Estimated risk of malignancy is 20%–30%.

\(^{i}\)The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (FLUS)) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see (PAP-1). If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation. Use molecular markers with caution and caveat.

\(^{j}\)Alternative terms include: rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%–10%.

\(^{m}\)Molecular diagnostics are not recommended for Hürthle cell neoplasm.

\(^{o}\)Clinical risk factors, sonographic patterns, and patient preference can help determine whether observation or lobectomy is appropriate.

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### FNA RESULTS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid lymphoma</td>
<td><strong>See NCCN Guidelines for B-cell Lymphomas</strong></td>
</tr>
<tr>
<td>Cystic</td>
<td>Correlate with ultrasound, re-aspirate suspicious areas</td>
</tr>
<tr>
<td>Insufficient biopsy, nondiagnostic</td>
<td>Repeat FNA with ultrasound guidance and immediate cytologic review for adequacy of specimen (preferred) or Consider surgery</td>
</tr>
<tr>
<td>Solid</td>
<td>• Observe if nodule growth, repeat FNA or consider surgery</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
</tr>
</tbody>
</table>

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*pInclused nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, and Hashimoto’s thyroiditis. Estimated risk of malignancy is approximately 5% or less; consider observation.*

*qRepeat ultrasound after 6–12 mo, if stable for 1–2 years, then subsequent ultrasound can be considered at 3- to 5-year intervals.*

*rGrowth defined as >50% increase in nodule volume or 20% increase in size of 2–3 dimensions. Size changes should be >2 mm and should be assessed by direct comparison of images.*

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PRINCIPLES OF THYROID-STIMULATING HORMONE (TSH) SUPPRESSION

• Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH.

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

  ▶ For low-risk patients with biochemical evidence but no structural evidence of disease (eg, Tg positive, but imaging negative), maintain TSH levels at 0.1–0.5 mU/L.

  ▶ Patients who remain disease free for several years can probably have their TSH levels maintained within the reference range.

• Given the potential toxicities associated with TSH-suppressive doses of levothyroxine—including cardiac tachyarrhythmias (especially in the elderly) and bone demineralization (particularly in post-menopausal women) as well as frank symptoms of thyrotoxicosis—the risk and benefit of TSH-suppressive therapy must be balanced for each individual patient.

• Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d).
PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA

- Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic medullary thyroid cancer (MTC) and in radio iodine-refractory differentiated thyroid cancer (DTC).  
  1,2,3

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

- The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient’s quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have 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.  
  4,5,6,7
In addition, dose modification may be required, including dose holds and dose reductions.

5Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician’s perspective. Semin Oncol 2014;41 Suppl 2:S1-S16.
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## Thyroid Carcinoma – Papillary Carcinoma

<table>
<thead>
<tr>
<th>FNA RESULTS</th>
<th>DIAGNOSTIC PROCEDURES</th>
<th>PREOPERATIVE OR INTRAOPERATIVE DECISION-MAKING CRITERIA</th>
<th>PRIMARY TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA</td>
<td></td>
<td>Indications for total thyroidectomy (any present):</td>
<td>Total thyroidectomy</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td>• Known distant metastases</td>
<td>Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Extrathyroidal extension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tumor &gt;4 cm in diameter</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cervical lymph node metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poorly differentiated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider for prior radiation exposure (category 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider bilateral nodularity</td>
<td></td>
</tr>
</tbody>
</table>

### Papillary carcinoma

- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- CT/MRI with contrast for fixed, bulky, or substernal lesions
- Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy)
- Consider FNA for suspicious lateral neck nodes

#### Indications for total thyroidectomy or lobectomy, if all criteria present:

- No prior radiation exposure
- No distant metastases
- No cervical lymph node metastases
- No extrathyroidal extension
- Tumor ≤4 cm in diameter

#### Total thyroidectomy (category 2B)

- Any of the following:
  - Tumor >4 cm
  - Positive resection margins
  - Gross extrathyroidal extension
  - Macroscopic multifocal disease
  - Macroscopic nodal metastasis
  - Vascular invasion

#### Lobectomy + isthmusectomy (category 2B)

- All of the following:
  - Negative margins
  - No contralateral lesion
  - NIFTP pathologic diagnosis

#### Completion of thyroidectomy

- Consider thyroglobulin measurement and anti-Tg antibodies 6–12 wks post-op
- Consider levothyroxine therapy to keep TSH low or normal

### Note

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**CLINICAL PRESENTATION**

Papillary carcinoma found post-lobectomy

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

**PRIMARY TREATMENT**

Any of the following:
- Tumor >4 cm
- Positive resection margins
- Gross extra-thyroidal extension
- Macroscopic multifocal disease
- Confirmed nodal metastasis<sup>d</sup>
- Confirmed contralateral disease
- Vascular invasion
- Poorly differentiated

Completion of thyroidectomy

- Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease
- Consider prophylactic central neck dissection (level VI) (category 2B)<sup>i</sup>

Completion of thyroidectomy

Tumor 1–4 cm in diameter or
Lymphatic invasion

Consider levothyroxine therapy to keep TSH low or normal<sup>h</sup>

Observe<sup>j</sup> (category 2B)

Consider levothyroxine therapy to keep TSH low or normal<sup>h</sup>

Observe<sup>j</sup>

All of the following:
- Negative resection margins
- No contralateral lesion
- Tumor <1 cm in diameter
- No suspicious lymph node

Completion of thyroidectomy or
Lymphatic invasion

See Postsurgical Evaluation (PAP-3)

See Surveillance and Maintenance (PAP-7)

<sup>d</sup>Completion thyroidectomy is not required for small volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm in largest dimension). See (PAP-4).

<sup>h</sup>See Principles of TSH Suppression (THYR-A).

<sup>i</sup>Possible benefit to reduce recurrence for patients with T3-T4 lateral disease must be balanced with risk of hypoparathyroidism and recurrent laryngeal nerve damage. See (PAP-1).

<sup>j</sup>Measurement of thyroglobulin and antithyroglobulin antibodies is useful for future follow-up and assessing trend patterns.

---

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

**No gross residual disease in neck**

- **Resectable** → Resect, if possible
  - No gross residual disease
    - **See Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (PAP-4)**

**Gross residual disease in neck**

- **Resectable** → Resect, if possible
  - **Suspected or proven inadequate RAI uptake**
    - TSH + Tg measurement + antithyroglobulin antibodies (6–12 wk postoperatively)
    - Total body radioiodine imaging (category 2B)

  - **Adequate RAI uptake**
    - Radioiodine treatment (preferred)
    - Post-treatment 131I whole body imaging
    - Consider EBRT/IMRT

- **Unresectable**
  - Observe or Consider External-beam radiation therapy (EBRT/IMRT) if disease is threatening vital structures

**Suppress TSH with levothyroxine**

- **See Surveillance and Maintenance (PAP-7)**

---

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

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

**Consideration for Initial Postoperative RAI Therapy after Total Thyroidectomy**

<table>
<thead>
<tr>
<th>RAI not typically recommended (if all present):</th>
<th>RAI not typically indicated, See (PAP-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Classic papillary thyroid carcinoma (PTC)</td>
<td></td>
</tr>
<tr>
<td>• Primary tumor &lt;2 cm</td>
<td></td>
</tr>
<tr>
<td>• Intrathyroidal</td>
<td></td>
</tr>
<tr>
<td>• Unifocal or multifocal</td>
<td></td>
</tr>
<tr>
<td>• No detectable anti-Tg antibodies</td>
<td></td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &lt;1 ng/mL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAI selectively recommended (if any present):</th>
<th>RAI being considered, See (PAP-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary tumor 2–4 cm</td>
<td></td>
</tr>
<tr>
<td>• High-risk histology*</td>
<td></td>
</tr>
<tr>
<td>• Lymphatic invasion</td>
<td></td>
</tr>
<tr>
<td>• Cervical lymph node metastases</td>
<td></td>
</tr>
<tr>
<td>• Macroscopic multifocality (one focus &gt;1 cm)</td>
<td></td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &lt;5–10 ng/mL ^</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAI typically recommended (if any present):</th>
<th>Amenable to RAI, See (PAP-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gross extrathyroidal extension</td>
<td></td>
</tr>
<tr>
<td>• Primary tumor &gt;4 cm</td>
<td></td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &gt;5–10 ng/mL ^</td>
<td></td>
</tr>
</tbody>
</table>

*Known or suspected distant metastases at presentation*  

<table>
<thead>
<tr>
<th>Gross residual disease not amenable to RAI therapy</th>
<th>See (PAP-9)</th>
</tr>
</thead>
</table>

\^Tg values obtained 6–12 weeks after total thyroidectomy.

\*ie. poorly differentiated, tall cell, columnar cell, and hobnail variants.

\^Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**RAI 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**
  - See (PAP-4)

- **Consider pretreatment $^{123}$I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH); (category 2B)$^{n,o}$

  - **Suspected$^{o,p}$ or proven thyroid bed uptake**
    - Follow without RAI ablation
    - or Selective use of RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)$^{q,r}$; post-treatment imaging (whole body RAI scan)
  - **Suspected$^{o,p}$ or proven radiiodine avid metastatic foci**
    - RAI therapy (100–200 mCi)$^{q,r}$; post-treatment imaging (whole body RAI scan)

- **No or minor thyroid bed uptake on scan, unstimulated Tg <1 ng/mL (with negative anti-Tg antibodies)**
  - Follow without RAI ablation
  - or Selective use of RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)$^{q,r}$; post-treatment imaging (whole body RAI scan)

**See Surveillance and Maintenance (PAP-7) and** Levothyroxine to appropriate TSH target **See (THYR-A)**

---

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

$^{o}$While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

$^{p}$Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

$^{q}$The administered activity of RAI therapy should be adjusted for pediatric patients.

$^{r}$If RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, 30 mCi of $^{131}$I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1–4 cm) with small-volume N1a disease (fewer than 3–5 metastatic lymph node metastases <0.5 cm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Known or suspected distant metastatic disease

6–12 weeks post-thyroidectomy → Known or suspected distant metastases at presentation
See (PAP-4)

Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci

Pretreatment $^{123}$I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)

Confirmed radiiodine-avid tumor

RAI therapy (100–200 mCi, or dose adjusted by dosimetry); post-treatment imaging (whole body RAI scan)

Consider RAI ablation/adjuvant therapy (30–100 mCi) post-treatment imaging (whole body RAI scan)

Cervical uptake only

See Surveillance and Maintenance (PAP-7) and Levothyroxine to appropriate TSH target
See (THYR-A)

QWhile pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

PClinically significant structural disease should be surgically resected if possible before radioiodine treatment.

QThe administered activity of RAI therapy should be adjusted for pediatric patients.

STo evaluate macroscopic metastatic foci for potential alternative therapies (such as surgical resection, external beam irradiation) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.

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

URhTSH may be used for elderly patients for when prolonged hypothyroidism may be risky.

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

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

<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-term surveillance</strong></td>
<td></td>
</tr>
<tr>
<td>NED</td>
<td>Patients treated with $^{131}$I ablation, with a negative ultrasound, stimulated Tg &lt;2 ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulated thyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging (CT or MRI with contrast, bone scan, chest x-ray) as clinically appropriate, may be considered if clinical suggestion of recurrent disease.</td>
</tr>
</tbody>
</table>

**Additional workup**

- In iodine-responsive tumors, if detectable Tg or distant metastases or soft tissue invasion on initial staging, radioiodine imaging every 12–24 mo until no clinically significant response is seen to RAI treatment (either withdrawal of thyroid hormone or rhTSH)$^x$

- If $^{131}$I imaging negative and stimulated Tg >2–5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT with contrast, chest CT with contrast)

---

$^a$A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

$^w$In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging.

$^x$If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH.

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**RECURRENT DISEASE**

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

  → Suppress TSH with levothyroxine<sup>h</sup>  
  → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (see PAP-7)

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

  → Consider radioiodine therapy with 100–150 mCi<sup>q</sup>
  → post-treatment <sup>131</sup>I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

  → Surgery (preferred) if resectable<sup>y</sup>
  → and/or
  → Radiiodine treatment,<sup>y</sup>
  → if radiiodine imaging positive
  → and/or
  → local therapies when available (ethanol ablation, radiofrequency ablation [RFA])
  → and/or
  → EBRT/IMRT, if radiiodine imaging negative for select patients not responsive to other therapies or
  → observation for low-volume disease that is stable and distant from critical structures

**Locoregional recurrence**

**Metastatic disease**

See Treatment of Metastatic Disease (PAP-9)

and/or

local therapies when available

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<sup>h</sup>See Principles of TSH Suppression (THYR-A).

<sup>q</sup>The administered activity of RAI therapy should be adjusted for pediatric patients.

<sup>y</sup>Preoperative vocal cord assessment, if central neck recurrence.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.\(^{aa}\)
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.\(^{bb,cc,dd}\)
- Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies\(^{ee}\) when available to metastatic lesions if progressive and/or symptomatic.
- Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.\(^{bb}\) (See PAP-7)

- Consider surgical palliation and/or EBRT/SBRT/other local therapies\(^{ee}\) when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage.
- Consider embolization or other interventional procedures as alternatives to surgical resection/EBRT/IMRT in select cases.
- Consider intravenous bisphosphonate or denosumab.\(^z\)
- Active surveillance may be appropriate in asymptomatic patients with indolent disease.\(^{bb}\) (See PAP-7)
- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.\(^{bb}\) While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.\(^{bb,cc,dd}\)

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy
- Continue to suppress TSH with levothyroxine\(^h\)

Iodine-refractory unresectable locoregional recurrent/persistent disease or Iodine-refractory soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)

Iodine-refractory metastatic bone metastases\(^z\)

CNS metastases

See (PAP-10)

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

\(^h^\)See Principles of TSH Suppression (THYR-A).
\(^z^\)Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
\(^aa^\)The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
\(^bb^\)Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
\(^cc^\)While not FDA approved for treatment of differentiated thyroid cancer, commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib (BRAF-positive), or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
\(^dd^\)Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
\(^ee^\)Ethanol ablation, cryoablation, RFA, etc.
TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred.
- For multiple CNS lesions, consider resection and/or radiotherapy, including image-guided radiotherapy.
- For progressive and/or symptomatic disease, consider lenvatinib (preferred), or sorafenib, and/or
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.
- Consider resection of distant metastases and/or EBRT/IMRT to metastatic lesions if progressive and/or symptomatic.

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2017
Thyroid Carcinoma – Follicular Carcinoma

FNA RESULTS

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT

Follicular neoplasm\(^a\) or Follicular lesion of undetermined significance (FLUS)\(^a\) See (THYR-3)

- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- CT/MRI with contrast for fixed, bulky, or substernal lesions\(^b\)
- Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy)\(^c\)

Total thyroidectomy if invasive cancer, metastatic cancer, or patient preference Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease

- Benign
- Papillary carcinoma
- Follicular carcinoma

Invasive cancer (extensive vascular invasion)

- Completion of thyroidectomy

Minimally invasive cancer\(^e\)

- NIFTP pathologic diagnosis\(^f\)

Liquid biopsy

- Benign
- Observe

Papillary carcinoma

See (PAP-2)

Levothyroxine therapy to keep TSH normal\(^g\)

See (PAP-3)

Completion of thyroidectomy

See Postsurgical Evaluation (FOLL-2)

Completion of thyroidectomy or Observe

Consider levothyroxine therapy to keep TSH low or normal\(^g\)

See Surveillance and Maintenance (FOLL-7)

LoMoection/isthmusectomy\(^d\)

\(^a\)The diagnosis of follicular carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics (category 2B) may be useful to allow reclassification of follicular lesions (follicular neoplasm or follicular lesions of undetermined significance (FLUS)) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing (category 2B) in conjunction with clinical and ultrasound features suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see (PAP-1). Use molecular markers with caution and caveat.

\(^b\)Use of iodinated contrast is required for optimal cervical imaging using CT, although iodinated contrast will delay treatment with RAI.

\(^c\)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.

\(^d\)RAI not recommended after lobectomy.

\(^e\)Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion (1-4) and often requires examination of at least 10 histologic sections to demonstrate.

\(^f\)Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), has been reclassified and only lobectomy is needed.

\(^g\)See Principles of TSH Suppression (THYR-A).

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

No gross residual disease in neck

Resectable

Resect, if possible

Gross residual disease

No gross residual disease

Suspected or proven inadequate RAI uptake

Adequate RAI uptake

Observe or Consider EBRT/IMRT if disease is threatening vital structures

 Suppress TSH with levothyroxine9

See Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (FOLL-3)

Suspected or proven inadequate RAI uptake

Adequate RAI uptake

No RAI imaging performed

Observe or Consider EBRT/IMRT if disease is threatening vital structures

Go to See Surveillance and Maintenance (FOLL-7)

Unresectable

Observed and Consider EBRT/IMRT if disease is threatening vital structures

Suppress TSH with levothyroxine9

See Surveillance and Maintenance (FOLL-7)

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

9See Principles of TSH Suppression (THYR-A).

See NCCN Guidelines Index

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Discussion

# NCCN Guidelines Version 2.2017
## Thyroid Carcinoma – Follicular Carcinoma

## CLINICOPATHOLOGIC FACTORS

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<th>RAI not typically recommended (if all present):</th>
<th>CONSIDERATION FOR INITIAL POSTOPERATIVE RAI THERAPY AFTER TOTAL THYROIDECTOMY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary tumor &lt;2 cm</td>
<td>RAI not typically indicated</td>
</tr>
<tr>
<td>• Intrathyroidal</td>
<td></td>
</tr>
<tr>
<td>• No vascular invasion</td>
<td></td>
</tr>
<tr>
<td>• Clinical N0</td>
<td></td>
</tr>
<tr>
<td>• No detectable anti-Tg antibodies</td>
<td>RAI ablation is recommended when the combination of individual clinical factors (such as the size of the primary tumor, histology, degree lymphatic invasion, lymph node metastases, postoperative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.</td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &lt;1 ng/mL&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>• Minor vascular invasion</td>
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<th>RAI recommended (if any present):</th>
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<tbody>
<tr>
<td>• Gross extrathyroidal extension</td>
<td></td>
</tr>
<tr>
<td>• Primary tumor &gt;4 cm</td>
<td>Amenable to RAI</td>
</tr>
<tr>
<td>• Extensive vascular invasion</td>
<td>See (FOLL-6)</td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &gt;5–10 ng/L&lt;sup&gt;h,i&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Known or suspected distant metastases at presentation

Gross residual disease not amenable to RAI therapy

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<sup>h</sup>Tg values obtained 6–12 weeks after total thyroidectomy.

<sup>i</sup>Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

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

---

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
RAI NOT TYPICALLY INDICATED BASED ON CLINICOPATHOLOGIC FEATURES

| Clinicopathologic findings that would not typically indicate routine RAI ablation | 6–12 weeks post-thyroidectomy |
| --- |
| • Unstimulated Tg |
| • Lateral neck ultrasound if not done preoperatively |

<table>
<thead>
<tr>
<th>Tg &gt;5–10 ng/mL (with negative anti-Tg antibodies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast)</td>
</tr>
<tr>
<td>Consider further surgery prior to RAI</td>
</tr>
<tr>
<td>Consider RAI ablation/adjuvant therapy; See (FOLL-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tg &lt;5–10 ng/mL (with negative anti-Tg antibodies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No concerning finding on neck ultrasound</td>
</tr>
<tr>
<td>Follow without RAI ablation and See Surveillance and Maintenance (FOLL-7) and Levothyroxine to appropriate TSH target See (THYR-A)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinically significant, indeterminate or suspicious cervical nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign FNA</td>
</tr>
<tr>
<td>Malignant FNA</td>
</tr>
<tr>
<td>Consider further surgery prior to RAI See (FOLL-2)</td>
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NCCN Guidelines Version 2.2017
Thyroid Carcinoma – Follicular Carcinoma

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 (See FOLL-3)

Consider pretreatment 123I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH); (category 2B)

No or minor thyroid bed uptake on scan, unstimulated Tg <1 ng/mL (with negative anti-Tg antibodies)

Follow without RAI ablation

Suspected or proven thyroid bed uptake

Follow without RAI ablation or RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)

Suspected or proven radioiodine-avid metastatic foci

RAI therapy (100–200 mCi)

Post-treatment imaging (whole body RAI scan)

See Surveillance and Maintenance (FOLL-7) and Levothyroxine to appropriate TSH target (See THYR-A)

kAlternatively, low-dose 131I (1–3 mCi) may be used.
lWhile pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.
mClinically significant structural disease should be surgically resected if possible before radioiodine treatment.
nThe administered activity of RAI therapy should be adjusted for pediatric patients.
oIf RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, 30 mCi of 131I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1–4 cm) with small-volume N1a disease (fewer than 3–5 metastatic lymph node metastases <0.5 in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

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

<table>
<thead>
<tr>
<th>Known or suspected distant metastases at presentation</th>
<th>Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci</th>
<th>Pretreatment ( ^{123}I ) diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)</th>
<th>Confirmed radioiodine-avid tumor</th>
<th>RAI therapy (100–200 mCi, or dose adjusted by dosimetry)(^a), post-treatment imaging (whole body RAI scan)</th>
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</table>

\(^a\)While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative finds, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

\(^m\)Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

\(^p\)To evaluate macroscopic metastatic foci for potential alternative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.

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

\(^r\)rhTSH may be used for elderly patients for whom prolonged hypothyroidism may be risky.

\(^s\)The administered activity of RAI therapy should be adjusted for pediatric patients.
### Thyroid Carcinoma – Follicular Carcinoma

#### Surveillance and Maintenance

<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NED</strong></td>
<td>Long-term surveillance</td>
</tr>
<tr>
<td></td>
<td>• Patients treated with $^{131}$I ablation, with a negative ultrasound, stimulated Tg &lt;2 ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulated thyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging (CT with contrast or MRI, bone scan, chest x-ray) as clinically appropriate, may be considered if clinical suggestion of recurrent disease.</td>
</tr>
<tr>
<td><strong>Abnormal findings</strong></td>
<td>Additional workup</td>
</tr>
<tr>
<td></td>
<td>• In iodine-responsive tumors, if detectable Tg or distant metastases or soft tissue invasion on initial staging, radioiodine imaging every 12–24 mo until no clinically significant response is seen to RAI treatment (either withdrawal of thyroid hormone or rhTSH)⁵</td>
</tr>
<tr>
<td></td>
<td>• If $^{131}$I imaging negative and stimulated Tg &gt;2–5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT with contrast, chest CT with contrast)</td>
</tr>
</tbody>
</table>

#### Note:
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⁴A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

⁵In 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.

⁶If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH.
NCCN Guidelines Version 2.2017
Thyroid Carcinoma – Follicular Carcinoma

RECURRENT DISEASE

- Stimulated Tg 1–10 ng/mL
- Non-resectable tumors
- Non-radioiodine responsive
  → Suppress TSH with levothyroxine⁹
  → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (See FOLL-7)

- Stimulated Tg >10 ng/mL and rising
- Scans (including PET) negative
  → Consider radioiodine therapy with 100–150 mCi¹⁰ and post-treatment ¹³¹I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy
  → Surgery (preferred) if resectable
  → Radioiodine treatment, if radioiodine imaging positive
  → local therapies when available (ethanol ablation, RFA)
  → EBRT/IMRT, if radioiodine imaging negative for select patients not responsive to other therapies
  → observation for low-volume disease that is stable and distant from critical structures

Locoregional recurrence

Metastatic disease

See Treatment of Metastatic Disease (FOLL-9)

and/or
local therapies when available

⁹See Principles of TSH Suppression (THYR-A).
¹⁰The administered activity of RAI therapy should be adjusted for pediatric patients.
¹¹Preoperative vocal cord assessment, if central neck recurrence.

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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.  
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.  
- Consider resection of distant metastases and/or EBRT/ SBRT/IMRT/other local therapies when available to metastatic lesions if progressive and/or symptomatic.  
- Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.  

- Consider surgical palliation and/or EBRT/SBRT/other local therapies when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage.  
- Consider embolization or other interventional procedures as alternatives to surgical resection/EBRT/IMRT in select cases.  
- Consider intravenous bisphosphonate or denosumab.  
- Active surveillance may be appropriate in asymptomatic patients with indolent disease.  

- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.  
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.  

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9See Principles of TSH Suppression (THYR-A).  
10Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.  
11The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.  
12Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.  
13While not FDA approved for treatment of differentiated thyroid cancer, commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF-positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.  
14Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.  
15Ethanol ablation, cryoablation, RFA, etc.

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NCCN Guidelines Version 2.2017
Thyroid Carcinoma – Follicular Carcinoma

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred.
  and/or
- For multiple CNS lesions, consider resection and/or radiotherapy, including image-guided radiotherapy.
  and/or
- For progressive and/or symptomatic disease, consider lenvatinib (preferred), or sorafenib,\(^y,dd\)
  and/or
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available
  small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if
  clinical trials or other systemic therapies are not available or appropriate,\(^z,aa,bb,dd\)
  and/or
- Consider resection of distant metastases and/or EBRT/IMRT to metastatic lesions if progressive and/or
  symptomatic.

\(^x\)The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
\(^y\)Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. [See Principles of Kinase Inhibitor Therapy (THYR-B)].
\(^aa\)While not FDA approved for treatment of differentiated thyroid cancer, commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib (BRAF-positive), or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
\(^bb\)Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
\(^dd\)After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.

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

- **No gross residual disease in neck**
  - **No gross residual disease**
    - **Resect, if possible**
      - **Resectable**
        - **Resect, if possible**
          - **No gross residual disease**

- **No gross residual disease in neck**
  - **Suspected or proven inadequate RAI uptake**
    - **Adequate RAI uptake**
      - **Observe or Consider EBRT/IMRT if disease is threatening vital structures**
      - **Radioiodine treatment (preferred)**
        - **Post-treatment \(^{131}I\) whole body imaging**
          - **Consider EBRT/IMRT**

- **Gross residual disease in neck**
  - **Unresectable**
    - **TSH + Tg measurement + antithyroglobulin antibodies (6–12 wk postoperatively)**
      - **Total body radioiodine imaging (category 2B)**
    - **No RAI imaging performed**
      - **Observe or Consider EBRT/IMRT if disease is threatening vital structures**
      - **Radioiodine treatment (preferred)**
        - **Post-treatment \(^{131}I\) whole body imaging**
          - **Consider EBRT/IMRT**

- **Gross residual disease in neck**
  - **Unresectable**
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---

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\(h\)See Principles of TSH Suppression (THYR-A).
### CLINICOPATHOLOGIC FACTORS

<table>
<thead>
<tr>
<th>RAI not typically recommended (if all present):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary tumor &lt;2 cm</td>
</tr>
<tr>
<td>• Intrathyroidal</td>
</tr>
<tr>
<td>• No vascular invasion</td>
</tr>
<tr>
<td>• Clinical N0</td>
</tr>
<tr>
<td>• No detectable anti-Tg antibodies</td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &lt;1 ng/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAI selectively recommended (if any present):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary tumor 2–4 cm</td>
</tr>
<tr>
<td>• Minor vascular invasion</td>
</tr>
<tr>
<td>• Cervical lymph node metastases</td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &lt;5–10 ng/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAI recommended (if any present):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gross extrathyroidal extension</td>
</tr>
<tr>
<td>• Primary tumor &gt;4 cm</td>
</tr>
<tr>
<td>• Extensive vascular invasion</td>
</tr>
<tr>
<td>• Postoperative unstimulated Tg &gt;5–10 ng/L</td>
</tr>
</tbody>
</table>

### CONSIDERATION FOR INITIAL POSTOPERATIVE RAI THERAPY

<table>
<thead>
<tr>
<th>RAI not typically indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>See (HÜRT-4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAI ablation is recommended when the combination of individual clinical factors (such as the size of the primary tumor, histology, degree of lymphatic invasion, lymph node metastases, postoperative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAI being considered</td>
</tr>
<tr>
<td>See (HÜRT-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amenable to RAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>See (HÜRT-6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gross residual disease not amenable to RAI therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>See (HÜRT-9)</td>
</tr>
</tbody>
</table>

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1Tg values obtained 6–12 weeks after total thyroidectomy.

2Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

---

For general principles related to RAI therapy, See (Discussion)
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Thyroid Carcinoma – Hürthle Cell Carcinoma

RAI NOT TYPICALLY INDICATED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy
Clinicopathologic findings that would not typically indicate routine RAI ablation (See HÜRT-3)

• Tg >5–10 ng/mL (with negative anti-Tg antibodies)
• No concerning findings on neck ultrasound

Consider additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast)
Consider further surgery prior to RAI
Consider RAI ablation/adjuvant therapy; See (HÜRT-5)

Follow without RAI ablation and See Surveillance and Maintenance (HÜRT-7) and Levothyroxine to appropriate TSH target (See THYR-A)

Clinically significant, indeterminate, or suspicious cervical nodes

Malignant FNA

Consider further surgery prior to RAI; See (HÜRT-2)

Benign FNA

Clinically significant, indeterminate, or suspicious cervical nodes

Unstimulated Tg
• Lateral neck ultrasound if not done preoperatively

Tg <5–10 ng/mL (with negative anti-Tg antibodies)
No concerning finding on neck ultrasound

Tg >5–10 ng/mL (with negative anti-Tg antibodies)

• Unstimulated Tg
• Lateral neck ultrasound if not done preoperatively

For example, round morphology, microcalcifications, multiplicity, or growing enlarging nodes.

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**NCCN Guidelines Version 2.2017**  
**Thyroid Carcinoma – Hürthle Cell Carcinoma**

### RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

<table>
<thead>
<tr>
<th>6–12 weeks post-thyroidectomy</th>
<th>Clinicopathologic findings prompting consideration for RAI, without gross residual disease or known distant metastasis <em>(See HÜRT-3)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinicopathologic findings</strong></td>
<td><strong>Consider pretreatment 123I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH);</strong> <em>(category 2B)</em></td>
</tr>
<tr>
<td><strong>findings prompting</strong></td>
<td><strong>Suspected(m,n) or proven thyroid bed uptake</strong></td>
</tr>
<tr>
<td><strong>consideration for RAI</strong></td>
<td><strong>Follow without RAI ablation</strong></td>
</tr>
<tr>
<td><strong>without gross</strong></td>
<td><strong>Follow without RAI ablation or RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)” post-treatment imaging (whole body RAI scan)</strong></td>
</tr>
<tr>
<td><strong>residual disease</strong></td>
<td><strong>Suspected(m,n) or proven radioiodine avid metastatic foci</strong></td>
</tr>
<tr>
<td><strong>or known distant</strong></td>
<td><strong>RAI therapy (100–200 mCi)” post-treatment imaging (whole body RAI scan)</strong></td>
</tr>
<tr>
<td><strong>metastasis</strong></td>
<td><strong>See Surveillance and Maintenance (HÜRT-7) and Levothyroxine to appropriate TSH target (See THYR-A)</strong></td>
</tr>
</tbody>
</table>

\( ^1 \)Alternatively, low-dose \( ^{131} \)I (1–3 mCi) may be used.

\( ^m \)While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.

\( ^n \)Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

\( ^o \)The administered activity of RAI therapy should be adjusted for pediatric patients.

\( ^p \)If RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, 30 mCi of \( ^{131} \)I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1–4 cm) with small-volume N1a disease (fewer than 3–5 metastatic lymph node metastases <0.5 in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

---

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Known or suspected distant metastatic disease

6–12 weeks post-thyroidectomy

Known or suspected distant metastases at presentation (See HÜRT-3)

Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci

Pretreatment ¹²³I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)

Confirmed radiiodine avid tumor

RAI therapy (100–200 mCi, or dose adjusted by dosimetry); post treatment imaging (whole body RAI scan)

Consider RAI ablation/adjuvant therapy (30–100 mCi); post treatment imaging (whole body RAI scan)

Central-cervical (remnant) uptake only

Levothyroxine to appropriate target (See THYR-A)

See Surveillance and Maintenance (HÜRT-7)

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Thyroid Carcinoma – Hürthle Cell Carcinoma

6–12 weeks post-thyroidectomy

Known or suspected distant metastases at presentation (See HÜRT-3)

Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci

Pretreatment ¹²³I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)

Confirmed radiiodine avid tumor

RAI therapy (100–200 mCi, or dose adjusted by dosimetry); post treatment imaging (whole body RAI scan)

Central-cervical (remnant) uptake only

Levothyroxine to appropriate target (See THYR-A)

See Surveillance and Maintenance (HÜRT-7)

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

**FINDINGS**

**MANAGEMENT**

**Long-term surveillance**

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound
- Consider TSH-stimulated or TSH-unstimulated Tg measurements using an ultrasensitive assay in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies
- Consider TSH-stimulated radioiodine whole body imaging in high-risk patients, patients with previous RAI-avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance

- Patients treated with $^{131}$I ablation, with a negative ultrasound, stimulated Tg <2 ng/mL (with negative antithyroglobulin antibodies), and negative RAI imaging (if performed) may be followed by unstimulated thyroglobulin annually and by periodic neck ultrasound. TSH-stimulated testing, or other imaging (CT or MRI with contrast, bone scan, chest x-ray) as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

**Recurrent disease** (See HÜRT-8)

**Additional workup**

- In iodine-responsive tumors, if detectable Tg or distant metastases or soft tissue invasion on initial staging, radioiodine imaging every 12–24 mo until no clinically significant response is seen to RAI treatment (either withdrawal of thyroid hormone or rhTSH)
- If $^{131}$I imaging negative and stimulated Tg >2–5 ng/mL, consider additional nonradioiodine imaging (eg, central and lateral neck compartments ultrasound, neck CT with contrast, chest CT with contrast)

**Metastatic disease** (See HÜRT-9)

**Abnormal findings**

- A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
- 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.
- If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH.

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**NCCN Guidelines Version 2.2017**

**Thyroid Carcinoma – Hürthle Cell Carcinoma**

**RECURRENT DISEASE**

- **Stimulated Tg 1–10 ng/mL**
  - **Non-resectable tumors**
  - **Non-radioiodine responsive**
    - Suppress TSH with levothyroxine
    - Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (see **HÜRT-7**)

- **Stimulated Tg >10 ng/mL and rising**
  - **Scans (including PET) negative**
    - Consider radioiodine therapy with 100–150 mCi
    - and
    - post-treatment $^{131}$I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

- **Locoregional recurrence**
  - Surgery (preferred) if resectable
    - Radioiodine treatment, if radioiodine imaging positive
    - Local therapies when available (ethanol ablation, RFA)
    - EBRT/IMRT, if radioiodine imaging negative for select patients not responsive to other therapies
    - Observation for low-volume disease that is stable and distant from critical structures

- **Metastatic disease**
  - See Treatment of Metastatic Disease (HÜRT-9)
  - and/or
  - local therapies when available

---

**h**See Principles of TSH Suppression (THYR-A).

**o**The administered activity of RAI therapy should be adjusted for pediatric patients.

**x**Preoperative vocal cord assessment, if central neck recurrence.

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**NCCN Guidelines Version 2.2017**

**Thyroid Carcinoma – Hürthle Cell Carcinoma**

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**TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY**

| Iodine-refractory unrectable loco-regional recurrent/persistent disease | For progressive and/or symptomatic disease, consider lenvatinib (preferred), or sorafenib. 
| --- | --- |
| or Iodine-refractory soft tissue metastases (e.g., lung, liver, muscle) excluding CNS metastases | While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate. 
| | Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies when available to metastatic lesions if progressive and/or symptomatic. 
| | Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis. 

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

- Continue to suppress TSH with levothyroxine

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**CNS metastases**

- See (HÜRT-10)

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### TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

**CNS metastases**

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred. and/or
- For multiple CNS lesions, consider resection and/or radiotherapy, including image-guided radiotherapy. and/or
- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib. and/or
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate. and/or
- Consider resection of distant metastases and/or EBRT/IMRT to metastatic lesions if progressive and/or symptomatic.

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2 The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.

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

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

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

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

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**Thyroid Carcinoma – Medullary Carcinoma**

**CLINICAL PRESENTATION**

- Basal serum calcitonin level
- CEA
- Pheochromocytoma screening<sup>b</sup>
- Serum calcium
- Consider genetic counseling
- Screen for RET proto-oncogene mutations<sup>c</sup> (exons 10, 11, 13–16)
- 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)<sup>d</sup>
- Consider contrast-enhanced CT of chest and liver MRI or 3-phase CT with contrast of liver<sup>e,f</sup>

**DIAGNOSTIC PROCEDURES**

- In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
- Evidence of pheochromocytoma should be evaluated and addressed appropriately before proceeding to the next step on the pathway.
- Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors).
- 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.
- Having distant metastases does not mean that surgery is contraindicated.
- Liver imaging is seldom needed if calcitonin <400 pg/mL.

**PRIMARY TREATMENT**

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

**Thresholds**

- ≥1.0 cm in diameter or bilateral thyroid disease
- <1.0 cm in diameter and unilateral thyroid disease

**Clinical Trials**

NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### CLINICAL PRESENTATION

Medullary thyroid carcinoma diagnosed after initial thyroid surgery

### ADDITIONAL WORKUP

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

### MANAGEMENT

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

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

---

*Germline mutation should prompt family testing of first-degree relatives and genetic counseling. ([See NCCN Guidelines for Neuroendocrine Tumors](https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf)).*

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

---

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## CLINICAL PRESENTATION

### MEN 2B
**Germline mutation of RET proto-oncogene**
- **(codon 918, 883, or compound heterozygous [V804M + E805K, Y806C, or S904C] RET mutations)**

### MEN 2A/Familial medullary thyroid carcinoma **(codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations)**

## ADDITIONAL WORKUP

### Basal serum calcitonin level

### CEA

### Pheochromocytoma screening

### Central and lateral neck compartments ultrasound, if not previously done

## PRIMARY TREATMENT

### Total thyroidectomy during the first year of life or at diagnosis

### Therapeutic neck dissection as indicated; consider prophylactic bilateral central neck dissection (level VI)

### Consider more extensive node dissection (levels II–V) if tumor(s) >0.5 cm in diameter

### Adjuvant EBRT/IMRT is rarely recommended

### Postoperative administration of levothyroxine to normalize TSH

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

See **Primary Treatment (MEDU-4)**

---

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---

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

*b* Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.

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

*d* The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less high risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandt ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)

*e* Normal calcitonin ranges have not been established for very young children.

*f* Screening for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A) should be performed annually. For some RET mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.
# Thyroid Carcinoma – Medullary Carcinoma

## Clinical Presentation

<table>
<thead>
<tr>
<th>MEN 2A/Familial medullary thyroid carcinoma (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations) (^{a,c,h})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No primary hyperparathyroidism</strong></td>
</tr>
<tr>
<td>Measure serum calcium ± PTH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary hyperparathyroidism</th>
</tr>
</thead>
</table>

## Primary Treatments

- **Total thyroidectomy by age 5\(^a,h\) or when mutation identified\(^a\) (if mutation identified at older age)**
- **Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin\(^k\) 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**
- **Adjuvant EBRT/IMRT is rarely recommended**
- **Postoperative administration of levothyroxine to normalize TSH**

### Notes

- The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less-high-risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)
- **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.**

---

\(^a\)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 family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)

\(^h\)The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less-high-risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)

\(^k\)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.

---

### Notes

**All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2017
Thyroid Carcinoma – Medullary Carcinoma

MANAGEMENT
2–3 MONTHS POSTOPERATIVE

**Detectable basal calcitonin or Elevated CEA**
- Basal calcitonin
- CEA

**Basal calcitonin undetectable and CEA within reference range**
- Neck ultrasound
- If calcitonin $\geq 150$ pg/mL, cross-sectional imaging should include contrast-enhanced CT (± PET) or MRI with contrast of the neck, chest, abdomen with liver protocol
- Bone scan in select patients

**Imaging positive or symptomatic disease**

**Imaging negative and asymptomatic**
- Serum calcitonin, CEA every 6–12 mo
- Additional studies or more frequent testing based on calcitonin/CEA doubling time
- No additional imaging required if calcitonin and CEA stable

**SURVEILLANCE**

**Positive result**
- Annual serum calcitonin, CEA
- Consider central and lateral neck compartments ultrasound
- Additional studies or more frequent testing if significantly rising calcitonin or CEA
- No additional imaging required if calcitonin and CEA stable
- For MEN 2B or 2A, annual biochemical screenings for pheochromocytoma and hyperparathyroidism (MEN 2A)

**Negative result**
- Continue observation

**See Recurrent or Persistent Disease (MEDU-6 and MEDU-7)**

**Positive result**
- Bone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels

**Negative result**
- Continue observation or Consider cervical reoperation, if primary surgery incomplete

**See Recurrent or Persistent Disease (MEDU-6 and MEDU-7)**

1The likelihood of significant residual disease with an undetectable basal calcitonin is very low.

mBone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.

nSee page (PHEO-I) from the NCCN Guidelines for Neuroendocrine Tumors.

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**NCCN Guidelines Version 2.2017**

**Thyroid Carcinoma – Medullary Carcinoma**

### RECURRENT OR PERSISTENT DISEASE LOCOREGIONAL DISEASE

**TREATMENT**

- Surgical resection is the preferred treatment modality
- or
- EBRT/IMRT can be considered for unresectable disease or, less commonly, after surgical resection
- or
- Consider vandetanib\(^o\) or cabozantinib (category 1)\(^o\) for unresectable disease that is symptomatic or progressing by RECIST criteria\(^q,r\)
- or
- Active surveillance

---

\(^o\)Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.

\(^p\)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.

\(^q\)Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.

See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).

\(^r\)Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

---

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**RECURRENT OR PERSISTENT DISEASE**

**DISTANT METASTASES**

<table>
<thead>
<tr>
<th>Asymptomatic disease</th>
<th>Observe or Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy), or vandetanib(o,p) (category 1), or cabozantinib(o) (category 1) if not resectable and progressing by RECIST criteria(q,r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic disease or progression(q)</td>
<td>Progressive disease, see pathway below</td>
</tr>
</tbody>
</table>

- **Vandetanib (category 1)\(s\)**
- **Cabozantinib (category 1)\(s\)**
- **Clinical trial**
- **Consider other small-molecule kinase inhibitors\(t\)**
- **Dacarbazine (DTIC)-based chemotherapy**
- **EBRT/IMRT for local symptoms**
- **Consider intravenous bisphosphonate or denosumab\(u\) therapy for bone metastases**
- **Consider palliative resection, ablation (eg, radiofrequency ablation, embolization, other regional therapy), or other regional treatment**
- **Best supportive care**

---

\(o\)Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.

\(p\)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.

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

\(r\)Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

\(s\)Clinical benefit can be seen in both sporadic and familial MTC.

\(t\)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, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib.

\(u\)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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### Anaplastic Thyroid Carcinoma (ATC)

#### FNA OR CORE BIOPSY FINDING

- CBC with differential
- Comprehensive chemistry
- TSH
- Neck ultrasound
- CT with contrast of head, neck, chest, abdomen, pelvis
- Laryngoscopy
- FDG PET/CT (skull base to mid-thigh)
- In case of airway invasion, bronchoscopy
- Direct exam of larynx
- Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)

#### ESTABLISH GOALS OF THERAPY

- Consultation with multidisciplinary management team
- Discuss prognosis
- Discuss risks/benefits of treatment options
- Discuss palliative care options

#### STAGE

**Stage IVA or IVB (Locoregional disease)**

- R0/R1 resection achieved (usually as incidentally discovered, very small ATC)
- Adjuvant EBRT/IMRT ± Chemotherapy

**Stage IVC (metastatic disease)**

- Incomplete (R2 resection)/Unresectable
- EBRT/IMRT ± Chemotherapy

**See (ANAP-2)**

---

*aConsider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary in order to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and lymphoma.

*bPreoperative 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.

*cSee Staging (ST-1).

*dVocal 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.

*eResectability for locoregional disease depends on extent of involved structures, potential morbidity, and mortality associated with resection. In most cases, there is no indication for a debulking surgery. See Staging (ST-1) for definitions of R0/R1/R2.

*fSee Systemic Therapy for Anaplastic Thyroid Carcinoma (ANAP-A).

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Thyroid Carcinoma – Anaplastic Carcinoma**

<table>
<thead>
<tr>
<th>METASTATIC DISEASE</th>
<th>TREATMENT</th>
<th>SURVEILLANCE AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Aggressive therapy →</td>
<td>• Total thyroidectomy with therapeutic lymph node dissection if resectable (R0/R1)</td>
</tr>
<tr>
<td>Palliative care →</td>
<td>• Locoregional radiation therapy</td>
<td>• Consider clinical trial</td>
</tr>
<tr>
<td></td>
<td>• Systemic therapy (See ANAP-A)</td>
<td>• Palliative locoregional radiation therapy</td>
</tr>
<tr>
<td></td>
<td>• Consider clinical trial</td>
<td>• Local lesion control with surgery or radiation (eg, bone&lt;sup&gt;g&lt;/sup&gt;, brain metastases)</td>
</tr>
<tr>
<td></td>
<td>• Palliative locoregional radiation therapy</td>
<td>• See NCCN Guidelines for Central Nervous System Cancers</td>
</tr>
<tr>
<td></td>
<td>• Hospice/Best supportive care</td>
<td></td>
</tr>
</tbody>
</table>

<sup>c</sup>See Staging (ST-1).

<sup>g</sup>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.

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### SYSTEMIC THERAPY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agents/Dosages</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/carboplatin</td>
<td>Paclitaxel 60–100 mg/m², carboplatin AUC 2 mg/m² IV</td>
<td>Weekly</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel 135–175 mg/m², carboplatin AUC 5–6 mg/m² IV</td>
<td>Every 3–4 weeks</td>
</tr>
<tr>
<td>Docetaxel/doxorubicin</td>
<td>Docetaxel 60 mg/m² IV, doxorubicin 60 mg/m² IV (with pegfilgrastim) or</td>
<td>Every 3–4 weeks</td>
</tr>
<tr>
<td></td>
<td>Docetaxel 20 mg/m² IV, doxorubicin 20 mg/m² IV</td>
<td>Weekly</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>60–90 mg/m² IV</td>
<td>Weekly</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>135–200 mg/m² IV</td>
<td>Every 3–4 weeks</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>60–75 mg/m² IV</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>20 mg/m² IV</td>
<td>Weekly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
<th>Residual Tumor (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TX</strong> No evidence of primary tumor</td>
<td><strong>NX</strong> Regional lymph nodes cannot be assessed</td>
<td><strong>M0</strong> No distant metastasis</td>
<td><strong>R0</strong> No residual tumor</td>
</tr>
<tr>
<td><strong>T1</strong> Tumor 2 cm or less in greatest dimension limited to the thyroid</td>
<td><strong>N0</strong> No regional lymph node metastasis</td>
<td><strong>M1</strong> Distant metastasis</td>
<td><strong>R1</strong> Microscopic residual tumor</td>
</tr>
<tr>
<td><strong>T1a</strong> Tumor 1 cm or less, limited to the thyroid</td>
<td><strong>N1</strong> Regional lymph node metastasis</td>
<td></td>
<td><strong>R2</strong> Macroscopic residual tumor</td>
</tr>
<tr>
<td><strong>T1b</strong> Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid</td>
<td><strong>N1a</strong> Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
<td></td>
<td><strong>Rx</strong> Presence of residual tumor cannot be determined</td>
</tr>
<tr>
<td><strong>T2</strong> Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid</td>
<td><strong>N1b</strong> Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Moderately advanced disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Very advanced disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All anaplastic carcinomas are considered T4 tumors.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Intrathyroidal anaplastic carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Anaplastic carcinoma with gross extrathyroid extension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification).
## Stage grouping:
Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma.

### Papillary or Follicular (differentiated)

#### Under 45 Years

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any</td>
<td>Any</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
</tr>
</tbody>
</table>

#### 45 Years and Older

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1a</td>
<td>M0</td>
</tr>
</tbody>
</table>

### Stage IVA

<table>
<thead>
<tr>
<th>T4a</th>
<th>N1a</th>
<th>M0</th>
</tr>
</thead>
</table>

### Stage IVB

<table>
<thead>
<tr>
<th>T4b</th>
<th>Any</th>
<th>M0</th>
</tr>
</thead>
</table>

### Stage IVC

<table>
<thead>
<tr>
<th>Any</th>
<th>T</th>
<th>Any</th>
<th>M1</th>
</tr>
</thead>
</table>

### Medullary Carcinoma (all age groups)

#### Stage I

| T1  | N0  | M0  |

#### Stage II

| T2  | N0  | M0  |
| T3  | N0  | M0  |

#### Stage III

| T1  | N1a | M0  |
| T2  | N1a | M0  |
| T3  | N1a | M0  |

### Anaplastic Carcinoma

All anaplastic carcinomas are considered Stage IV

#### Stage IVA

| T4a | Any | M0 |

#### Stage IVB

| T4b | Any | M0 |

#### Stage IVC

| Any | T   | Any | M1 |

### Histopathologic Type

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit [www.springer.com](http://www.springer.com).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.
Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

Epidemiology

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the U.S. population for individuals ages 50 years and older. 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. 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.

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%. It is estimated that approximately 56,870 new cases of thyroid carcinoma will be diagnosed in the United States in 2017. As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men. Thyroid carcinoma is currently the fifth most common malignancy diagnosed in women. The disease is also diagnosed more often in white North Americans than in African Americans. Although thyroid carcinoma can occur at any age, the peak incidence is approximately age 50 years.

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. An average of 63,229 patients per year were diagnosed with thyroid carcinoma from 2010 to 2014. Of these 63,229 patients, 89.4% had papillary carcinoma, 4.6% had follicular carcinoma, 2.0% had Hürthle cell carcinoma, 1.7% had medullary carcinoma, and 0.8% had anaplastic carcinoma.

5-year relative survival rates for patients with papillary and follicular carcinomas (stages I–III) were 98% and 90%, respectively.

In 2017, it is estimated that approximately 2010 cancer deaths will occur among persons with thyroid carcinoma in the United States. Anaplastic carcinoma is almost uniformly lethal; however, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases. Thyroid carcinoma occurs more often in women; however, mortality rates are lower for younger women. Although the estimated incidence of thyroid carcinoma previously increased by an average of ~5% annually between 2004 and 2013, the incidence rate has recently stabilized, likely due to more conservative indications for thyroid biopsy. Because overall mortality has not dramatically increased since 1975 (1150 vs. 2010 deaths), the previous increase in incidence may reflect, at least in part, earlier detection of subclinical disease (ie, small papillary carcinomas). However, data show the incidence has increased by varying degrees across all tumor sizes and age groups. The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma address management for the different types of thyroid carcinoma including papillary, follicular, Hürthle cell, medullary, and anaplastic carcinoma. Additional sections in these NCCN Guidelines® include Nodule Evaluation, Principles of Thyroid-Stimulating Hormone (TSH) Suppression, Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma, and the AJCC staging tables. 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. These NCCN Guidelines for Thyroid
Carcinoma are updated at least once a year and are available at NCCN.org. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the NCCN Panel during the process of developing these guidelines.

Literature Search Criteria and Guidelines Update Methodology
Prior to the update of this version of the NCCN Guidelines for Thyroid Carcinoma, an electronic search of the PubMed database was performed to obtain key literature in thyroid carcinoma published between October 8, 2015 and November 11, 2016, 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 only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 168 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

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

Radiation-Induced Thyroid Carcinoma
Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma. 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. The risk for radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma. 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.

Adults have a very small risk of developing thyroid carcinoma after exposure to 131I. After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary carcinomas after being exposed to 131I fallout. It became evident that 131I and
other short-lived 131IIs were potent thyroid carcinogens in these children, particularly those younger than 10 years of age when they were exposed. Iodine deficiency increases the risk for radiation-induced thyroid cancer. 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. 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. Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their diagnosis. About 50% of the malignant nodules are discovered during a routine physical examination, by serendipity on imaging studies, or during surgery for benign disease. The other 50% are usually first noticed by the patient, usually as an asymptomatic nodule. Regrettably, the typically indolent nature of differentiated thyroid carcinoma often leads to long delays in diagnosis that may substantially worsen the course of the disease.

**Initial Workup**

For a patient with a thyroid nodule, the first step is to measure the serum thyrotropin (thyroid-stimulating hormone [TSH]) level and to do an ultrasound of the thyroid and neck; all nodules (even incidentalomas) should have this assessment; there is no size cutoff. The TSH level, ultrasound results, and clinical features are used to determine whether is it necessary to do fine-needle aspiration (FNA) of the nodule or whether there is a low risk of malignancy (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma).

FNA, with or without ultrasound guidance, is the procedure of choice for evaluating suspicious thyroid nodules. Data show that higher TSH levels are associated with an increased risk for differentiated thyroid carcinoma in patients with thyroid nodules, although TSH and thyroglobulin (Tg) do not appear to be useful for screening for thyroid cancer. FNA should be considered in patients with normal or elevated TSH, certain ultrasound features, and clinical findings. FNA of clinically significant or suspicious cervical lymph nodes should also be considered if identified in the ultrasonographic evaluation of the thyroid and neck. Ultrasound features that increase the threshold for FNA are described in the NCCN algorithm (see Sonographic Features in Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). RAI imaging is recommended in patients with low TSH.

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

In the setting of a multinodular thyroid gland, selection of nodules for FNA should be based on the pattern of radiographic features that predict a higher likelihood of malignancy, such as the previous example, or based on growth of a nodule over time. Similarly, choosing which nodules are appropriate for active surveillance rather than FNA should be based on the pattern of ultrasound features that predict benignity (eg, spongiform appearance, a pure cyst, specific intranodular appearances) or small size due to treatment considerations as previously noted. At the time of thyroid ultrasound, a critical feature that should be assessed is the presence or absence of concerning lymphadenopathy in the central and lateral neck. The presence of a node with concerning characteristics (eg, hypoechoic, rounded, absent of fatty hilum, cystic or partially cystic, microcalcifications) should lead to FNA of the node rather than, or in addition to, the most concerning thyroid nodule.

Thyroid nodules smaller than 1 cm occur with such frequency in the asymptomatic general population that they are often found by serendipity when performing imaging studies for other head or neck problems. Often termed “incidentalomas,” nodules smaller than 1 cm are typically clinically insignificant lesions and usually do not require FNA, unless there are suspicious findings (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). In selected cases, it may be reasonable to follow these nodules with serial ultrasounds. Data indicate that older patients with intrathyroidal papillary microcarcinomas may be good candidates for an active surveillance approach (rather than immediate surgery) and usually show no evidence of clinically significant disease progression over at least 5 to 10 years of follow-up. These observations cast doubt on the clinical benefit of diagnosing (and treating) papillary microcarcinoma in these selected groups. Others feel that surgery should be considered for select patients with papillary carcinomas who are 45 years of age or older.

The NCCN Panel uses recommendations from several organizations (eg, American Thyroid Association [ATA], Society of Radiologists in Ultrasound, NCI) and their expertise when formulating the NCCN Guidelines for thyroid nodules (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). The NCCN recommendations describe which nodules require further assessment with FNA and which can undergo active surveillance. In 2015, the ATA updated its guidelines on the management of thyroid nodules and thyroid cancer; its comprehensive guidelines also discuss ultrasound and FNA. In 2007, the NCI had a conference on using FNA to manage thyroid nodules. The NCI guidelines discuss which nodules should undergo FNA and discuss the FNA results (ie, carcinoma, benign). The Society of Radiologists in Ultrasound wrote a consensus statement in 2005 about management of thyroid nodules identified at thyroid ultrasonography. Its recommendations describe which nodules should undergo FNA based on nodule size and ultrasound characteristics, and on clinical features that might predict risk of morbidity from an undiagnosed malignancy. Suspicious criteria by ultrasound include increased central hypervascularty, hypoechoic mass, microcalcifications, infiltrative margins, and other features (see Sonographic Features in Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma).

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present (see Nodule Evaluation in the
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. Family history of thyroid cancer is also indicative of malignancy. If 2 or more of these features are present, the likelihood of thyroid cancer is virtually assured; however, this is a rare situation. A patient's age and gender also affect the probability of malignancy. Other factors that increase the suspicion of malignancy include: 1) a history of head and neck irradiation; 2) a history of diseases associated with thyroid carcinoma, such as familial adenomatous polyposis (formerly called Gardner’s syndrome), Carney complex, Cowden’s syndrome, and multiple endocrine neoplasia (MEN) types 2A or 2B; 3) evidence of other thyroid cancer–associated diseases or syndromes, such as hyperparathyroidism, pheochromocytoma, marfanoid habitus, and mucosal neuromas (suggestive of MEN2B), which make the presence of medullary carcinoma more likely; or 4) the presence of suspicious findings detected by imaging, such as focal FDG uptake on PET or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.

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

**FNA Results**

Cytologic examination of an FNA specimen is typically categorized as: 1) carcinoma (papillary, medullary, or anaplastic) or suspicious for carcinoma; 2) follicular or Hürthle cell neoplasm; 3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); 4) thyroid lymphoma; 5) benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto’s thyroiditis); or 6) insufficient biopsy (nondiagnostic) (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). These diagnostic categories for FNA results reflect the NCI’s state of the science conference held in 2007. 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.

Molecular diagnostic testing to detect individual mutations (eg, BRAF V600E, RET/PTC, RAS, PAX8/PPAR [peroxisome proliferator-activated receptors] gamma) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions. The BRAF V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation. Although controversial, data suggest that BRAF V600E mutations may predict for increased recurrence of
papillary carcinoma. The choice of the precise molecular test depends on the cytology and the clinical question being asked. Indeterminate groups include: 1) follicular or Hürthle cell neoplasms; and 2) AUS/FLUS. The NCCN Panel recommends molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). Molecular diagnostic testing is not recommended for suspected Hürthle cell neoplasms. Molecular diagnostic testing may include multigene assays (eg, the gene expression classifier) or individual mutational analysis. The gene expression classifier measures the expression of at least 140 genes. BRAF V600E mutation analysis was recommended by some panelists for the evaluation of thyroid nodules (not restricted to the follicular lesions). Furthermore, a majority of the panelists would recommend BRAF V600E testing in the evaluation of follicular lesions. A minority of panelists expressed concern regarding observation of follicular lesions because they were perceived as potentially pre-malignant lesions with a very low, but unknown, malignant potential if not surgically resected (leading to recommendations for either observation or considering lobectomy in lesions classified as benign by molecular testing). Clinical risk factors, sonographic patterns, and patient preference can help determine whether observation or lobectomy is appropriate for these patients (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma).

Rather than proceeding to immediate surgical resection to obtain a definitive diagnosis for these indeterminate FNA cytology groups (follicular lesions), patients can be followed with observation 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 for FNA can vary widely between institutions. 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.

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of medullary carcinoma. 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. Metastatic renal carcinoma can mimic follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma. 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 January 2016 and reflects the 2010 staging (7th edition) from the AJCC (see Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland on the CAP website). Follicular and Hürthle cell carcinomas are rarely diagnosed by FNA, because the diagnostic criterion for these malignancies requires
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demonstration of vascular or capsular invasion. 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. Approximately 20% of these lesions are malignant. Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful for follicular cell carcinomas (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma).

In some patients with follicular lesions, serum TSH level and thyroid 123I or 99m technetium scanning may identify patients with an autonomously functioning or “hot” nodule who often may be spared surgery, because the diagnosis of follicular adenoma (ie, benign) is highly likely. Patients who are clinically euthyroid with a low TSH and a hot nodule on thyroid imaging should be evaluated and treated for thyrotoxicosis as indicated even when cytology is suspicious for follicular neoplasm. Those with a hypofunctional (cold or warm) nodule and with suspicious clinical and sonographic features should proceed to surgery (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). Those patients with an increased or normal TSH and with cytology suspicious for follicular or Hürthle cell neoplasm should undergo diagnostic lobectomy or total thyroidectomy, depending on patient preference unless molecular diagnostic testing predicts a low risk of malignancy.

In patients with follicular or Hürthle cell neoplasm on FNA who are selected for thyroid surgery in order to obtain a definitive diagnosis, total thyroidectomy is recommended for bilateral disease, unilateral disease greater than 4 cm (especially in men), invasive cancer, metastatic cancer, or if the patient prefers this approach. An FNA that yields insufficient cellular material for diagnosis and is solid should be repeated, because approximately 50% of subsequent specimens are adequate to assign a diagnosis (see Nodule Evaluation in the NCCN Guidelines for Thyroid Carcinoma). Data suggest that ultrasound-guided FNA may be useful in diagnosing thyroid carcinoma, especially when repeating an FNA for a previously nondiagnostic biopsy. In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules. Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of significant growth. Significant nodule growth is defined as a greater than 50% increase in nodule volume or 20% increase in size of 2-3 dimensions. Size changes should be greater than 2 mm and assessed by direct comparison of images. When a diagnosis of thyroid carcinoma is promptly established using FNA, the tumor is often confined to the thyroid or has metastasized only to regional nodes; thus, patients can be cured. However, as many as 5% of patients with papillary carcinoma and up to 10% of those patients with follicular or Hürthle cell carcinoma have tumors that aggressively invade structures in the neck or have produced distant metastases. Such cancers are difficult to cure.

Recurrence of Differentiated Thyroid Carcinoma
Depending on initial therapy and other prognostic variables, up to 30% of patients with differentiated thyroid carcinoma may have tumor recurrences during several decades; 66% of these recurrences occur within the first decade after initial therapy. Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome. 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. 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.
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 (e.g., 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. 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.

Prognosis

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular carcinomas, patient age at the time of initial therapy and tumor stage are important. Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in men. Thyroid carcinoma is more lethal in patients older than 40 years of age, increasingly so with each subsequent decade of life. The mortality rate increases dramatically after age 60 years. However, tumor recurrence shows a remarkably different behavior with respect to age. Recurrence frequencies are highest (40%) for those younger than 20 years or older than 60 years; recurrence at other ages ensues in only about 20% of patients. This disparity between cancer-related mortality and the frequency of tumor recurrence probably accounts for most of the disagreements among clinicians concerning optimal treatment for patients with differentiated thyroid carcinoma. How clinicians assess the importance of tumor recurrence (as opposed to cancer-specific survival) accounts for much of the debate surrounding the influence of age on the treatment plan for children and young adults.

Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good. 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. 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. 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. Prognosis is less favorable in men than in women, but the difference is usually small. 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. Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.

Familial Syndromes

Familial, non-medullary carcinoma accounts for about 5% of papillary thyroid carcinoma (PTCs) and, in some cases, may be clinically more aggressive than the sporadic form. For patients to be considered as having familial papillary carcinoma, most studies require at least 3 first-degree relatives to be diagnosed with papillary carcinoma because the finding of cancer in a single first-degree relative may just be a chance event. Microscopic familial papillary carcinoma tends to be multifocal and bilateral, often with vascular invasion, lymph node metastases, and high rates of recurrence and distant metastases.
Other familial syndromes associated with papillary carcinoma are familial adenomatous polyposis, Carney complex (multiple neoplasia and lentiginis syndrome, which affects endocrine glands), and Cowden’s syndrome (multiple hamartomas). 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. The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, BRAF V600E mutation status, and metastases. For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence. 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). In patients with sporadic medullary carcinoma, a somatic RET oncogene mutation confers an adverse prognosis.

**Histology**

Although survival rates with typical papillary carcinoma are quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors. A well-defined tumor capsule, which is found in about 10% of PTCs, is a particularly favorable prognostic indicator. A worse prognosis is associated with: 1) anaplastic tumor transformation; 2) tall-cell papillary variants, which have a 10-year mortality of up to 25%; 3) columnar variant papillary carcinoma (a rapidly growing tumor with a high mortality rate); and 4) diffuse sclerosing variants, which infiltrate the entire gland. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), formerly known as 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. NIFTP tumors have a low risk for adverse outcomes and, therefore, require less aggressive treatment. NIFTP was reclassified to prevent overtreatment of this indolent tumor type as well as the psychological consequences of a cancer diagnosis on the patient. Molecular diagnostic testing may be useful for diagnosing NIFTP.

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. 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. FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma. 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). 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. The poor prognosis is closely related to older age at the time of diagnosis, advanced tumor stage, and larger tumor size. 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.

When Hürthle (oncocytic) cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as Hürthle cell carcinoma, although the WHO classification and the AJCC consider it as a variant of follicular thyroid carcinoma. Molecular studies suggest, however, that this tumor may be more similar to papillary than to follicular thyroid carcinomas. 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. 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. In 2 large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, about twice the frequency of follicular thyroid carcinoma metastases. In contrast to papillary or follicular carcinomas, 131I may be not effective in patients with Hürthle cell carcinoma because fewer Hürthle cell carcinomas concentrate 131I. In a series of 100 patients with distant metastases, 131I uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell carcinomas. In the National Cancer Data Base report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.

**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. 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. 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, which may be the presenting feature and also may be associated with distant metastases. 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. In fact, the prognosis for papillary and follicular thyroid carcinomas is incrementally poorer as tumors increase in size. There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas.

**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.\textsuperscript{12,180} Recurrence rates are 2 times higher with locally invasive tumors, and as many as 33\% of patients with such tumors die of cancer within a decade.\textsuperscript{12,181}

**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.\textsuperscript{129} An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.\textsuperscript{182} The prognostic importance of regional lymph node metastases is controversial.\textsuperscript{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).\textsuperscript{183} Older patients (>45 years) with papillary carcinoma and lymph node metastases also have decreased survival.\textsuperscript{184} A 2012 review by Randolph et al emphasized the correlation between the size and number of metastatic lymph nodes and the risk of recurrence.\textsuperscript{185} 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.\textsuperscript{186,187} About 50\% of these metastases are present at the time of diagnosis.\textsuperscript{129} Distant metastases occur even more often in patients with Hürthle cell carcinoma (35\%) and in those patients who are older than age 40 years at diagnosis.\textsuperscript{172,173} Among 1231 patients in 13 studies, the sites of reported distant metastases were lung (49\%), bone (25\%), both lung and bone (15\%), and the central nervous system (CNS) or other soft tissues (10\%). The main predictors of outcome for patients with distant metastases are patient’s age, the site of the distant metastasis, and whether the metastases concentrate 1\textsuperscript{31}I.\textsuperscript{172,173,188,189}

Although some patients, especially younger ones, with distant metastases survive for decades, about 50\% die within 5 years regardless of tumor histology.\textsuperscript{129} Even so, some pulmonary metastases are compatible with long-term survival.\textsuperscript{190} 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.\textsuperscript{191} The survival rates are highest in young patients with diffuse lung metastases seen only on 1\textsuperscript{31}I imaging and not on x-ray.\textsuperscript{189,191,192} Prognosis is worse with large pulmonary metastases that do not concentrate 1\textsuperscript{31}I.\textsuperscript{172,173,188}

**Tumor Staging**

The NCCN Guidelines for Thyroid Carcinoma do not use TNM stages as the primary determinant of management. Instead, many characteristics of the tumor and patient play important roles in these NCCN Guidelines. Many specialists in thyroid cancer also follow this paradigm. When treating differentiated thyroid carcinoma, many clinicians place a stronger emphasis on potential morbidity than on mortality (see Surgical Complications in this Discussion). Staging was revised in the 2002 AJCC guidelines (6\textsuperscript{th} edition) for patients with papillary and follicular carcinomas who are older than 45 years of age.\textsuperscript{193} Note that the AJCC considers Hürthle cell carcinoma as a variant of follicular carcinoma, as does the WHO.\textsuperscript{9} The current 2010 AJCC staging guidelines (7\textsuperscript{th} edition) for thyroid carcinoma may be useful for prognosis (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma).\textsuperscript{9} Many studies (including those described in this
Discussion) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition\textsuperscript{194} and not the 6th or 7th editions.\textsuperscript{9,193}

**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.\textsuperscript{9,127,133,193,195} 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.\textsuperscript{179} 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.\textsuperscript{133}

Unfortunately, a study that classified 269 patients with papillary carcinoma according to 5 different prognostic paradigms found that some patients in the lowest-risk group from each approach died of cancer.\textsuperscript{136} This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.\textsuperscript{193,196} 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 45 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,\textsuperscript{197,198} 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.\textsuperscript{127,199}

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.\textsuperscript{3,200-203} 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.\textsuperscript{204} This allows ongoing re-assessment of risk and allows the management paradigm to be better tailored to realistic estimates of risk that may change substantially over time.

**Surgical Management of Differentiated Thyroid Carcinoma**

**Ipsilateral Lobectomy Versus Total Thyroidectomy**

The appropriate extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk papillary carcinoma, which is reflected in the NCCN category 2B recommendations for these procedures (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma and *Papillary Thyroid Carcinoma* in this Discussion). In most clinical settings, decisions about the extent of thyroidectomy should be individualized and done in consultation with the patient.\textsuperscript{205} Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring\textsuperscript{135} 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 $\leq$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.\(^{206}\)

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.\(^{207}\) No significant differences were found in cancer-specific mortality or distant metastasis rates between the 2 groups. However, the 20-year frequencies of local recurrence and nodal metastasis after unilateral lobectomy were 14% and 19%, respectively, which were significantly higher (\(P = .0001\)) than the frequencies of 2% and 6% seen after bilateral thyroid lobe resection. Hay et al concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk papillary carcinoma.\(^{207}\)

Most NCCN Panel Members recommend total thyroidectomy for patients with biopsy-proven papillary carcinoma who have large-volume pathologic N1 metastases (\(>5\) involved nodes with metastases \(>2\) mm in largest dimension),\(^{3,34,208}\) because this procedure is associated with improved disease-free survival.\(^{12,137,207,209}\) Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.\(^{129,206}\) After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and 131I therapy)\(^{12}\) and the highest frequency (11%) of subsequent pulmonary metastases.\(^{210}\) However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.\(^{41}\) Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.\(^{12}\)

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.\(^{134,195,211}\) The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole-body 131I imaging. Panel members recommend total lobectomy (without radioactive iodine RAI ablation) for patients with papillary carcinoma who have small-volume pathologic N1A metastases (\(<5\) involved nodes with no metastasis \(>2\) mm, in largest dimension).\(^{212}\)

NCCN Panel Members believe that total lobectomy alone is adequate treatment for papillary microcarcinomas provided the patient has not been exposed to radiation, has no other risk factors, and has a tumor smaller than 1 cm that is unifocal and confined to the thyroid without vascular invasion (see Primary Treatment in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).\(^{3,12,175,213-216}\) Total lobectomy alone is also adequate treatment for NIFTP pathologies (see Tumor Variables Affecting Prognosis, Histology) and minimally invasive follicular thyroid carcinomas (see Primary Treatment in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). However, completion thyroidectomy is recommended for any of the following: tumor more than 4 cm in diameter, positive resection margins, gross extrathyroidal extension, macroscopic multifocal disease, macroscopic nodal metastases, confirmed contralateral disease, or vascular invasion.\(^3\) Note that “gross extrathyroidal extension” refers to spread of the primary tumor outside of the thyroid capsule with invasion into the surrounding structures such as strap muscles, trachea, larynx, vasculature, esophagus, and/or recurrent laryngeal nerve.\(^{149,217,218}\)
Completion Thyroidectomy
This procedure is recommended when remnant ablation is anticipated or if long-term follow-up is planned with serum Tg determinations and with (or without) whole-body 131I imaging. Large thyroid remnants are difficult to ablate with 131I.210 Completion thyroidectomy has a complication rate similar to that of total thyroidectomy. Some experts recommend completion thyroidectomy for routine treatment of tumors 1 cm or larger, because approximately 50% of patients with cancers this size have additional cancer in the contralateral thyroid lobe.180,219-225 In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.222

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.137 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.223

Surgical Complications
The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy.205 Transient clinical hypoparathyroidism after surgery is common in adults226 and children137,227 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.228 One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.229 Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.230 When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5860 patients found that surgeons who performed more than 100 thyroidectomies a year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies a year had 4 times as many complications.231

Radioactive Iodine Therapy
Postoperative Radioactive Iodine (RAI)
The NCCN Panel recommends a selective use approach to postoperative RAI administration. The 3 general, but overlapping, functions of postoperative RAI administration include: 1) ablation of the normal thyroid remnant, which may help in surveillance for recurrent disease (see below); 2) adjuvant therapy to try to eliminate suspected micrometastases; or 3) RAI therapy to treat known persistent disease. The NCCN Guidelines have 3 different pathways for postoperative RAI administration based on clinicopathologic factors: 1) RAI typically recommended; 2) RAI selectively recommended; and 3) RAI not typically recommended (see Clinicopathologic Factors in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).

Postoperative RAI is typically recommended for patients at high risk of having persistent disease remaining after total thyroidectomy and includes patients with any of the following factors: 1) gross extrathyroidal extension; 2) a primary tumor greater than 4 cm; or 3) postoperative unstimulated Tg greater than 5 to 10 ng/mL (see Clinicopathologic Factors in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).

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

Guidelines from the ATA list very similar indications for postoperative RAI use and also provide specific guidance regarding the safe use of RAI in the outpatient setting. Studies show decreased recurrence and disease-specific mortality for populations at intermediate or higher risk when postoperative 131I therapy is administered as part of the initial treatment. In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was about 3-fold higher in patients either treated with thyroid hormone alone or given no postoperative medical therapy when compared with patients who underwent postoperative thyroid remnant ablation with 131I (P < .001). Moreover, fewer patients developed distant metastases (P < .002) after thyroid remnant 131I ablation than after other forms of postoperative treatment. However, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter. 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 (hazard risk, 0.71; 95% CI, .62-.82; P < .001). Some studies have found that remnant ablation had less of a therapeutic effect, perhaps because more extensive locoregional surgery had been done. Previously, it was reported that postoperative RAI was associated with decreased overall survival in patients with stage I thyroid cancer, although the deaths seemed unrelated to thyroid cancer. Longer follow-up suggests that overall survival is not decreased or increased in these patients. However, a more recent study reported that the incidence of secondary malignancies, such as leukemia and salivary gland malignancies, has increased in patients with low-risk thyroid cancer (ie, T1N0) who received RAI. Debate continues about ablating the thyroid bed with 131I after total thyroidectomy. In patients with papillary carcinoma who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates. A long-term study (n=1298) found that overall survival is not improved in patients who receive RAI ablation. Reasons favoring remnant ablation include: 1) simplified patient follow-up, because elimination of thyroid bed uptake prevents misinterpretation of it as disease; 2) elimination of normal tissue as a source of Tg production, which facilitates identification of patients who are free of disease and may simplify their care while promoting early identification of those with residual cancer; and 3) elimination of normal tissue, which may eliminate the nidus for continued confounding anti-Tg antibody production. Conversely, others argue that most recurrences can be easily detected with neck ultrasound and that serum Tg levels are often quite low after a total thyroidectomy. Therefore, in patients at low and intermediate risk, the clinical benefit of routine remnant ablation as a requirement for optimal follow-up remains uncertain.

Data suggest that lower doses of RAI are as effective as higher doses—30 versus 100 mCi—for ablating in patients with low-risk thyroid cancer (eg, T1b/T2 [1–4 cm], clinical N0 disease). The NCCN Guidelines reflect a more cautious approach to using RAI ablation based on these randomized trials. If RAI ablation is used, the NCCN Guidelines...
recommend (category 1) 30 mCi of 131I for RAI ablation in patients at low risk based on these randomized trials. This same ablation dose—30 mCi—may be considered (category 2B) in patients at slightly higher risk (see RAI Being Considered Based on Clinicopathologic Features in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).\textsuperscript{245} 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.\textsuperscript{246} The possible benefits of RAI should be weighed with the risk of adverse effects as part of treatment decision making.\textsuperscript{244} Adverse effects may be minimized by using lower doses of RAI.\textsuperscript{32}

**Diagnostic Total Body Imaging and Thyroid Stunning**

When indicated, diagnostic total body 131I imaging is recommended (category 2B) after surgery to assess the completeness of thyroidectomy and to assess whether residual disease is present (see RAI Being Considered Based on Clinicopathologic Features in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma). However, a phenomenon termed “stunning” may occur when imaging doses of 131I induce follicular cell damage.\textsuperscript{247} Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent 131I.\textsuperscript{248}

To avoid or reduce the stunning effect, the following have been suggested: 1) the use of 123I or small (2 or 3 mCi) doses of 131I; and/or 2) a shortened interval (≤72 hours) between the diagnostic 131I dose and the therapy dose. However, 123I is more expensive and smaller 131I doses have reduced sensitivity when compared with larger 131I doses.\textsuperscript{247-249} In addition, a large thyroid remnant may obscure detection of residual disease with 131I imaging. Some experts recommend that diagnostic 131I imaging be avoided completely with decisions based on the combination of tumor stage and serum Tg.\textsuperscript{247} Other experts advocate that whole-body 131I diagnostic imaging may alter therapy, for example: 1) when unsuspected metastases are identified; or 2) when an unexpectedly large remnant is identified that requires additional surgery or a reduction in RAI dosage to avoid substantial radiation thyroiditis.\textsuperscript{3,247,250-252} Thus, NCCN Panel Members disagreed about using diagnostic total body 131I imaging before postoperative RAI, which is reflected in the category 2B recommendation for imaging.\textsuperscript{3,253-255} Note that diagnostic imaging is used less often for patients at low risk.

**Postoperative Administration of RAI**

Historically, the 3 methods of determining 131I therapy activities (doses) have included: empiric fixed doses, quantitative dosimetry, and upper-bound limits that are set by blood dosimetry.\textsuperscript{3,247,250,256,257} 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 lesion dosimetry. In the past, hospitalization was required to administer therapeutic doses of 131I greater than 30 mCi (1110 MBq). However, hospitalization is no longer necessary in most states, because a change in federal regulations permits the use of much larger 131I doses in patients who are ambulatory.\textsuperscript{256} However, 131I therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses. Administration of a fixed dose of 131I is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of 131I in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of 131I. Lymph node metastases may be treated with about 100 to 175...
mCi (3700–6475 MBq) of 131I. 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 131I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in the elderly and in those with impaired kidney function.\textsuperscript{258,259} Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of 131I (which is very uncommon) are treated with 150 mCi of 131I (5550 MBq) or less to avoid lung injury, which may occur when more than 80 mCi remains in the whole body 48 hours after treatment. The administered activity of RAI therapy should be adjusted for pediatric patients.\textsuperscript{3,260-262} A pilot study demonstrated that targeted therapy of the MAP kinase pathway with a MEK inhibitor (selumetinib) significantly increased the effectiveness of RAI therapy in patients who were previously RAI refractory.\textsuperscript{263}

**Post-Treatment 131I Imaging**

When 131I therapy is given, whole-body 131I imaging should be performed several days later to document 131I uptake by the tumor. Post-treatment whole-body 131I imaging should be done, primarily because up to 25% of images show lesions that may be clinically important, which were not detected by the diagnostic imaging.\textsuperscript{256} In a study of pre-treatment and post-treatment imaging, the 2 differed in 27\% of the treatment cycles, but only 10\% of the post-treatment imaging showed clinically significant new foci of metastatic disease.\textsuperscript{264} Post-treatment imaging was most likely to reveal clinically important new information in patients younger than 45 years who had received 131I therapy in the past. Conversely, in older patients and patients who had not previously received 131I therapy, post-treatment imaging rarely yielded new information that altered the patient’s prognosis.\textsuperscript{264}

**Assessment and Management After Initial Treatment**

Serum Tg determinations, neck ultrasound, and whole-body 131I imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation.\textsuperscript{265} In contrast, neither serum Tg nor whole-body 131I imaging is specific for thyroid carcinoma in patients who have not undergone thyroidectomy and remnant ablation. When initial ablative therapy has been completed, serum Tg should be measured periodically. Serum Tg can be measured while the patient is taking thyroxine, but the test is more sensitive when thyroxine has been stopped or when recombinant human TSH (rhTSH) is given to increase the serum TSH.\textsuperscript{266,267}

Using current Tg assays, patients with measurable serum Tg levels during TSH suppression and those with stimulated Tg levels more than 2 ng/mL are likely to have residual/recurrent disease that may be localized in almost 50\% promptly and in an additional 30\% over the next 3 to 5 years.\textsuperscript{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) 131I imaging could be performed to detect residual thyroid tissue or carcinoma. However, patients dislike thyroid hormone withdrawal, because it causes symptomatic hypothyroidism. An alternative to thyroid hormone withdrawal is the administration of rhTSH intramuscularly, which stimulates thyroidal 131I uptake and Tg release.
while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism. Administration of rhTSH is well tolerated; nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects. It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.

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

**Measuring Serum Tg and Anti-Tg Antibodies**

Serum Tg measurement is the best means of detecting thyroid tissue, including carcinoma. Tg can be measured when TSH has been stimulated—either by thyroid hormone withdrawal or by rhTSH—because in this setting, serum Tg has a lower false-negative rate than whole-body 131I imaging. Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or rhTSH stimulation. Serum Tg generally does not increase as much after rhTSH administration as after withdrawal of thyroid hormone. The conditions for rhTSH–stimulated, whole-body 131I imaging stipulate using 4-mCi 131I doses (based on the trial) 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]). It is useful to measure serum Tg and anti-Tg antibody levels for follow-up and assessing trend patterns.

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

Anti-Tg antibodies should be measured in the same serum sample taken for Tg assay, because these antibodies (which are found in ≤25% of patients with thyroid carcinoma) invalidate serum Tg measurements in most assays. 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.

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. In patients with coexistent autoimmune thyroid disease at the time of surgery,
anti-Tg antibodies may persist far longer. In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for up to 20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.° Patients with persistently undetectable serum Tg and anti-Tg antibody levels have longer disease-free survival when compared with patients who have detectable levels.279

**Treating Patients With Positive Tg and Negative Imaging**

Post-treatment 131I imaging may indicate the location of metastases when the serum Tg level is increased, but a tumor [or metastases] cannot be found by physical examination or other localizing techniques such as diagnostic 131I imaging, neck ultrasonography, CT, MRI, or PET. Pulmonary metastases may be found only after administering therapeutic doses of 131I and obtaining whole-body imaging within a few days of treatment.280 In a study of 283 patients treated with 100 mCi (3700 MBq) of 131I, 6.4% had lung and bone metastases detected after treatment that had been suspected based on high serum Tg concentrations alone but that had not been detected after 2-mCi (74 MBq) diagnostic imaging.281

Unfortunately, most patients who are diagnostic imaging–negative and Tg-positive are not rendered disease free by 131I therapy; however, the tumor burden may be diminished.282 Thus, most patients with residual or recurrent disease confined to the neck undergo re-operation rather than RAI therapy in the hopes of a cure. RAI therapy is more commonly considered for those with distant metastases or inoperable local disease. Patients not benefiting from this therapy can be considered for clinical trials, especially those patients with progressive metastatic disease. When a large tumor is not visible on diagnostic whole-body imaging, its ability to concentrate 131I is very low; thus, the tumor will not respond to 131I therapy.

**Thyroid Hormone Suppression of TSH**

The use of 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.°,250,283,284 However, the optimal serum levels of TSH have not been defined because of a lack of specific data; therefore, the NCCN Panel recommends tailoring the degree of TSH suppression to the risk of recurrence and death from thyroid cancer for each individual patient. For patients with known residual carcinoma or those at high risk for recurrence, the recommended TSH level is below 0.1 milliunits/L. For patients at low risk and for those patients with an excellent response to initial therapy who are in remission, the recommended TSH level is either slightly below or slightly above the lower limit of the reference range. The risk and benefit of TSH-suppressive therapy must be balanced for each individual patient because of the potential toxicities associated with TSH-suppressive doses of levothyroxine, including cardiac tachyarrhythmias (especially in the elderly), bone demineralization (particularly in post-menopausal women), and frank symptoms of thyrotoxicosis.285 An adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d) is recommended for patients whose TSH levels are chronically suppressed. However, reports do not suggest that bone mineral density is altered in patients receiving levothyroxine.286,287

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated with thyroid hormone suppressive therapy.12,235,238,284,288-290 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. 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). One retrospective study reported a benefit of adjuvant EBRT after RAI in patients older than 40 years of age with invasive papillary carcinoma (T4) and lymph node involvement (N1). 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. Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of papillary carcinoma. Similarly, patients with microscopic residual papillary carcinoma after surgery are more commonly rendered disease free after receiving EBRT (90%) than those who do not receive it (26%). In another study, patients with microscopically invasive follicular thyroid carcinoma after surgery were also more often disease free when postoperative EBRT was given (53%) than when it was not given (38%). However, these patients had not received RAI. Similar benefit was shown with RAI alone in comparable patients treated with RAI after surgery. 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. Other data from single institutions also show that adjuvant EBRT yields long-term control of locoregional disease. Studies suggest that intensity-modulated radiation therapy (IMRT) is safe, effective, and less morbid in patients with thyroid cancer.

**External-Beam RT and Surgical Excision of Metastases**

Surgical excision, EBRT, stereotactic body radiation therapy (SBRT), or other local therapies can be considered for symptomatic isolated skeletal metastases or those that are asymptomatic in weight-bearing sites. Brain metastases pose a special problem, because 131I therapy may induce cerebral edema. Neurosurgical resection can be considered for brain metastases. For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery is preferred over whole brain radiation. 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. Most recurrent tumors respond well to surgery; 131I therapy; EBRT, SBRT, or IMRT; or other local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA).

**Systemic Therapy**

Systemic therapy can be considered for tumors that are not surgically resectable; are not responsive to 131I; are not amenable to EBRT treatment, SBRT, IMRT, or other local therapies; and have clinically significant structural disease progression during the last 6 to 12 months. Among 49 patients with metastatic differentiated thyroid carcinoma who were treated with 5 chemotherapy protocols, only 2 (3%) patients had
objective responses. In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin. Combination chemotherapy is not clearly superior to doxorubicin therapy alone. Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease. Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated. Agents include multitargeted kinase inhibitors, such as lenvatinib, sorafenib, sunitinib, axitinib, everolimus, vandetanib, cabozantinib, and pazopanib; and BRAF V600E mutation inhibitors, such as vemurafenib and dabrafenib. Data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in patients with papillary carcinoma who have ALK gene fusion.

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. Lenvatinib and sorafenib are recommended for the treatment of patients with RAI-refractory differentiated thyroid cancer (see Papillary Thyroid Carcinoma in this Discussion and the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Vandetanib and cabozantinib, oral kinase inhibitors, are recommended for the treatment of medullary carcinoma in patients with unresectable locally advanced or metastatic disease (see Medullary Thyroid Carcinoma in this Discussion and the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, stroke, and liver toxicity; however, most side effects can be managed and are reversible with discontinuation of the drug. Dose modifications of kinase inhibitors may be required. Pazopanib has been reported to cause reversible hypopigmentation.

**Papillary Thyroid Carcinoma**

**Surgical Therapy**

Imaging is performed before surgery to ascertain the extent of disease and to aid in the surgical decision-making process. A cervical ultrasound, including the thyroid and the central & lateral compartments, is the principal imaging modality that is recommended. 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. Surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients. In more than 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects. Preoperative ultrasound findings altered the operation in more than 40% of cases. In another report, operative management was altered in 23% of the total group due to findings on the preoperative ultrasound. These studies indicate that preoperative ultrasound has a high sensitivity for nodal disease and will detect nonpalpable nodal metastases in 20% to 33% of patients, and ultrasound should alter the index operation in a similar percentage of patients. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases. Cross-sectional imaging (CT or MRI) should be performed if the thyroid lesion is fixed, bulky, or substernal. Iodinated contrast is required for optimal cervical imaging with CT, although iodinated contrast will delay treatment with RAI. Evaluation of vocal cord mobility may be considered for patients with abnormal voice, a surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Vocal cord mobility may be evaluated.
by ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy.\textsuperscript{368}

The NCCN Panel agreed on the characteristics of patients at higher risk who require total thyroidectomy and neck dissection as the primary treatment (see Preoperative or Intraoperative Decision-Making Criteria in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).\textsuperscript{3,369,370} A total thyroidectomy is recommended for patients with any one of the following factors, including: known distant metastases, extrathyroidal extension, tumor greater than 4 cm in diameter, cervical lymph node metastases, or poorly differentiated histology. Total thyroidectomy may be considered for patients with bilateral nodularity or a prior exposure to radiation (category 2B for radiation exposure). Clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level VI dissection. In the lateral compartment, a formal modified radical neck dissection including levels II, III, IV, and Vb should be performed.\textsuperscript{371} Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Based on the results of a randomized controlled trial, the panel does not recommend prophylactic central neck dissection if the cervical lymph nodes are clinically negative. This trial of 181 patients with PTC randomized patients to receive either total thyroidectomy alone or total thyroidectomy plus central neck dissection and showed no difference in outcomes between the two groups.\textsuperscript{372} Central neck dissection will be required ipsilateral to a modified radical neck dissection done for clinically involved lateral neck lymph nodes in most cases. Selective dissection of individual nodal metastases (ie, cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field.

The NCCN Panel did not uniformly agree about the preferred primary surgery for patients with PTC who are assumed to be at lower risk of cancer-specific mortality. As previously mentioned, the extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk PTC, which is reflected in the NCCN category 2B recommendations for these procedures (see Ipsilateral Lobectomy Versus Total Thyroidectomy in this Discussion). Lobectomy plus isthmusectomy is recommended for patients who cannot (or refuse to) take thyroid hormone replacement therapy for the remainder of their lives.\textsuperscript{205} Note that some patients prefer to have total thyroidectomy to avoid having a second surgery (ie, completion thyroidectomy). Other patients prefer to have a lobectomy in an attempt to avoid thyroid hormone replacement therapy.

A study of more than 5000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for patients at low and high risk.\textsuperscript{373} 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.\textsuperscript{374} However, most guidelines (eg, NCCN, ATA) do not recommend active surveillance for patients with PTC.\textsuperscript{3} Another study of 2784 patients with differentiated thyroid carcinoma (86% with PTC) found that total thyroidectomy was associated with increased survival in patients at high risk.\textsuperscript{238} A study in 52,173 patients found that total thyroidectomy reduces recurrence rates and improves survival in patients with PTC of 1 cm or more when compared with lobectomy.\textsuperscript{375} For patients at lower risk who undergo lobectomy plus isthmusectomy, completion of thyroidectomy is recommended for any one of the following risk factors: large tumor (>4 cm), positive resection margins, gross extrathyroidal extension,
Thyroid Carcinoma

Macroscopic multifocal disease, vascular invasion, or macroscopic nodal metastases. While a retrospective study using the National Cancer Database has shown that a sizable percentage of patients with differentiated thyroid cancer receive RAI therapy following lobectomy\(^{376}\), the panel does not support this practice due to a lack of data showing benefit. Therefore, RAI is not recommended following lobectomy for differentiated thyroid cancer.

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

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). For example, RAI may be recommended when the primary tumor is 1 to 4 cm, but the final decision depends on the combination of individual clinical factors as outlined in the NCCN Guidelines. 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).

Therapy with 131I is typically recommended for patients with: 1) gross extrathyroidal extension; 2) primary tumor greater than 4 cm; or 3) postoperative unstimulated Tg greater than 5 to 10 ng/mL. All patients should be examined, and palpable neck disease should be surgically resected before any RAI treatment. A negative pregnancy test is required before the administration of RAI in women of child-bearing potential. The administered activity of RAI therapy should be adjusted for pediatric patients.\(^{262}\) RAI is not typically recommended for patients with either unifocal or multifocal papillary microcarcinomas (<2 cm) confined to the thyroid, and clinical N0 and M0.\(^{244}\) The NCCN Panel agrees that postoperative RAI administration after total thyroidectomy is not needed for patients with classic PTC with small-volume N1a disease if the postoperative unstimulated Tg levels are less than 1 ng/mL, 131I imaging is negative, there are no concerning findings on ultrasound, and anti-Tg antibody level is negative. RAI is selectively recommended if any of the following are present: 1) primary tumor 2 to 4 cm; 2) poorly...
differentially histology, tall cell, columnar cell, and hobnail variants; 3) lymphatic invasion; 4) cervical lymph node metastases; 5) macroscopic multifocality (ie, one focus >1 cm); or 6) postoperative unstimulated Tg less than 5 to 10 ng/mL. For patients with suspected or proven RAI-responsive residual tumor, RAI treatment is recommended (100–200 mCi) followed by post-treatment imaging; dosimetry can be considered for distant metastases (see RAI Being Considered Based on Clinicopathologic Features in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).

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

**Surveillance and Maintenance**

The recommendations for surveillance and maintenance are described in the algorithm (see Surveillance and Maintenance in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). About 85% of patients are considered to be low risk after surgery for papillary thyroid cancer. 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. Patients treated with 131I ablation may be followed with unstimulated Tg annually and with periodic neck ultrasound if they have negative ultrasounds, stimulated Tg less than 2 ng/mL (with negative anti-Tg antibodies), and negative RAI imaging (if performed). However, if they have a clinical suggestion of recurrent disease, then TSH-stimulated testing (or other imaging) may be considered. A subgroup of patients at low risk (eg, micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic neck ultrasound follow-up (without stimulated Tg or follow-up whole-body imaging) as long as their basal Tg remains low (see Surveillance and Maintenance in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories. Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.

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

The NCCN Panel agrees that surgery is the preferred therapy for locoregional recurrent disease if the tumor is resectable (see Recurrent Disease in the NCCN Papillary [Thyroid] Carcinoma algorithm). Cervical ultrasound, including the central and lateral compartments, is the principal imaging modality when locoregional recurrence is suspected. 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.

Clinically significant nodal recurrence in a previously undissected nodal basin should be treated with a formal compartmental resection. In the central neck, this is usually achieved through a unilateral level VI dissection and, occasionally, a level VII dissection. In the lateral compartment, a formal modified radical neck dissection—including levels II, III, IV, and Vb—should be performed. Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Selective dissection of individual nodal metastases (cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field, and is not recommended in the NCCN 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 a focused resection of the region of recurrence.

For unresectable locoregional recurrence, RAI treatment and EBRT or IMRT are recommended if the 131I imaging is positive. Local therapies, such as ethanol ablation or RFA, are also an option if available. EBRT or IMRT alone is another option in the absence of 131I uptake for select patients not responsive to other therapies.

When recurrent disease is suspected based on high serum-stimulated Tg values (>10 ng/mL) and negative imaging studies (including PET scans), RAI therapy can be considered using an empiric fixed dose of 100 to 150 mCi of 131I (see Recurrent Disease in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). The NCCN Panel had a major disagreement about recommending (category 3) post-treatment 131I 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 131I on the basis of increased Tg measurements alone. In a long-term follow-up study, no survival advantage was associated with empiric high-dose RAI in patients with negative imaging. 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. Observation may be considered for patients with low-volume disease that is stable and distant from critical structures.

Metastatic Disease Not Amenable to RAI Therapy

For metastatic disease not amenable to RAI therapy, several therapeutic approaches are recommended, depending on the site and number of tumor foci (see Treatment of Metastatic Disease Not Amenable to RAI Therapy in the NCCN Guidelines for Papillary
[Thyroid] Carcinoma. Patients should continue to receive levothyroxine to suppress TSH levels. For skeletal metastases, consider surgical palliation for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are EBRT, SBRT, or other local therapies. 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. Embolization (or other interventional procedures) of metastases can also be considered either prior to resection or as an alternative to resection.

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

For clinically progressive or symptomatic disease, recommended options include: 1) lenvatinib (preferred) or sorafenib; 2) clinical trials for non-131I–responsive tumors; 3) consider other non-FDA approved small molecule kinase inhibitors or systemic therapy if a clinical trial is not available; or 4) consider resection of distant metastases and/or EBRT or IMRT. The recommendations for lenvatinib (preferred) or sorafenib are based on phase 3 randomized trials. 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. 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.

Lenvatinib was compared with placebo in patients with metastatic differentiated thyroid cancer that was refractory to RAI in a phase 3 randomized trial. Patients receiving lenvatinib had a progression-free survival (PFS) of 18.3 months compared with 3.6 months for those receiving placebo (hazard ratio [HR], 0.21; 99% CI, 0.14–0.31; \( P < .001 \)). Six treatment-related deaths occurred in the lenvatinib group.

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

Other commercially available small-molecule kinase inhibitors may also be considered for progressive and/or symptomatic disease—including axitinib, everolimus, pazopanib, sunitinib, vandetanib, cabozantinib, or vemurafenib (for BRAF-positive disease)—although none have 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. Active surveillance is often appropriate for asymptomatic patients with indolent disease and no brain metastasis.
Because chemotherapy is usually not effective for non-RAI avid tumors, the NCCN Guidelines recommend clinical trials for treatment of these tumors; small molecule kinase inhibitors (ie, axitinib, sunitinib, pazopanib, vandetanib) or traditional cytotoxic systemic therapy can be considered if a trial is not available. However, kinase inhibitor therapy may be most appropriate for patients with unresectable recurrent disease that is threatening vital structures or is not responsive to EBRT or IMRT. Hypothyroidism has been reported in some patients receiving sunitinib or sorafenib, but it also seems to be associated with increased PFS.

**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. Unlike PTC, FNA is not specific for follicular thyroid carcinoma and accounts for the main differences in management of the 2 tumor types. The cytologic diagnosis of “[suspicious for] follicular neoplasm” will prove to be a benign follicular adenoma in 80% of cases. However, 20% of patients with follicular neoplasms on FNA are ultimately diagnosed with follicular thyroid carcinoma when the final pathology is assessed. Molecular diagnostic testing may be useful to determine the status of follicular lesions or lesions of indeterminate significance (including follicular neoplasms, AUS, or FLUS) as more or less likely to be malignant based on the genetic profile. Further diagnostic and treatment decisions for patients who present with follicular neoplasms are based on their TSH levels (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

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

Completion thyroidectomy is also recommended for tumors that, on final histologic sections after lobectomy plus isthmusectomy, are identified as minimally invasive follicular thyroid carcinomas. Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or few (1-4) foci of vascular invasion and often requires examination of at least 10 histologic sections. Minimally invasive cancers, as well as NIFTP tumors, may also be simply followed carefully, because minimally invasive follicular carcinomas and NIFTP usually have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma do occasionally occur. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see *Recurrent Disease* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

The other features of management and follow-up for follicular thyroid carcinoma are similar to those of PTC. Clinicopathologic factors can be used to guide decisions about whether to administer initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 2 to 4 cm, but the final
decision depends on the combination of individual clinical factors as outlined in the algorithm. 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 for suspected or proven thyroid bed uptake; alternatively, patients fitting these criteria may be followed without RAI ablation. 131I ablation and post-treatment imaging (with consideration of dosimetry for distant metastasis) is recommended for suspected or proven 131I-avid metastatic foci (see RAI Being Considered Based on Clinicopathologic Features in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). The decision to perform diagnostic whole-body 131I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before 131I therapy is administered is a category 2B recommendation for both follicular thyroid carcinoma and PTC because of the problem of stunning (see section on Diagnostic Total Body Imaging and Thyroid Stunning in this Discussion).

Hürthle Cell Carcinoma

This tumor (also known as oxyphilic cell carcinoma) is usually assumed to be a variant of follicular thyroid carcinoma,\(^{9,166}\) although the prognosis of Hürthle cell carcinoma is worse.\(^{171,399,401,403,404}\) Molecular diagnostic testing is not currently recommended for Hürthle cell carcinomas due to a lack of evidence showing benefit for molecular testing in this tumor type. The Hürthle cell variant of PTC is rare and seems to have a prognosis similar to follicular carcinoma.\(^{405}\)

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 131I (see Papillary Thyroid Cancer: Surgical Therapy in this Discussion).\(^{406}\) Postoperative EBRT or IMRT can be considered for: 1) unresectable primary Hürthle cell lesions that do not concentrate 131I if disease is threatening vital structures; and 2) unresectable locoregional recurrence (see Postsurgical Evaluation and Recurrent Disease in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma), similar to the management for follicular thyroid carcinoma.\(^3\)

Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see Clinicopathologic Factors in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 2 to 4 cm, but the final decision about whether to use RAI depends on the combination of individual clinical factors as outlined in the algorithm. 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 131I imaging. 131I therapy (100–150 mCi) may be considered after thyroidectomy for patients with stimulated Tg levels of more than 10 ng/mL who have negative scans (including FDG-PET) (see Recurrent Disease in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). Pretreatment diagnostic imaging (123I or low-dose 131I) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) may be considered based on pathology, postoperative Tg, and intraoperative findings (see RAI Being Considered Based on Clinicopathologic Features in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). However, some NCCN Panel Members did not feel that diagnostic total body imaging should be recommended before 131I therapy is administered, because the thyroid remnant may interfere with the scan, making this a category 2B recommendation.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid. Sporadic MTC accounts for about 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as: 1) MEN type 2A (MEN 2A), which is the most common type; and 2) MEN 2B. Familial MTC is now viewed as a variant of MEN 2A. Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of the disease tend to present at earlier ages. The 5-year relative survival for stages I to III is about 93%, whereas 5-year survival for stage IV is about 28%. 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. Distant metastases in the lungs or bones cause symptoms in 5% to 10% of patients. Many patients with advanced MTC can have diarrhea, Cushing’s syndrome, or facial flushing, because the tumor can secrete calcitonin and sometimes other hormonally active peptides (ie, adrenocorticotropic hormone [ACTH], calcitonin gene-related peptide [CGRP]). Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms. 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. However, routine measurement of the basal serum calcitonin concentration is not recommended by the NCCN Panel for evaluating a patient with nodular thyroid disease because of the expense of screening all thyroid nodules and only finding a few cases of MTC, the lack of confirmatory pentagastrin stimulation testing, and the resulting need for thyroidectomy in some patients who actually have benign thyroid disease. The ATA is equivocal about routine calcitonin measurement.
**Inherited MTC**

For patients in known kindreds with inherited MTC, prospective family screening with testing for mutant RET genes can identify disease carriers long before clinical symptoms or signs are noted. 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 and because pentagastrin is no longer available in the United States. When MEN 2A is suspected, the NCCN Guidelines recommend measurement of calcium levels with (or without) serum intact parathyroid hormone levels (see Additional Workup in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade of life, without gender preference. In patients with MEN 2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.

All familial forms of MTC and MEN 2 are inherited in an autosomal-dominant fashion. Mutations in the RET proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of familial MTC. The RET proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN 2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; MEN 2B and some familial MTC mutations are found within the intracellular exons 14 to 16. Somatic mutations in exons 11, 13, and 16 have also been found in at least 25% of sporadic MTC tumors—particularly the codon 918 mutation that activates the tyrosine kinase function of the receptor—and are associated with poorer prognosis of the patient.

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

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 (MEN 2A and 2B) and hyperparathyroidism (MEN 2A). Before surgery for MTC, it is important to diagnose and address coexisting pheochromocytoma to avoid hypertensive crisis during surgery (see Pheochromocytoma/Paraganglioma in the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org). Pheochromocytoma can be removed using laparoscopic adrenalectomy. Preoperative thyroid and neck ultrasound (including central and lateral neck compartments) is recommended. Contrast-enhanced CT of chest and liver MRI or 3-phase CT of liver can be considered, although distant metastasis does not contraindicate surgery. Liver imaging is rarely needed if the calcitonin is less than 400 pg/mL. Evaluation of vocal cord mobility can also be considered for patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
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) (7th edition of the AJCC Cancer Staging Manual). Staging for MTC slightly changed in the 2010 AJCC update (ie, 7th edition of the AJCC Cancer Staging Manual). In the 7th edition, T3, N0, M0 has been downstaged from stage III to stage II. All follow-up studies (in this Discussion) reporting on AJCC-TNM staging have referred to the 5th edition and not to the 6th or 7th editions. As previously mentioned, the 5-year relative survival for stages I to III MTC is about 93%, whereas 5-year survival for stage IV is about 28%. However, the TNM staging classification lacks other important prognostic factors. 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. 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. Despite an even younger typical age at diagnosis, however, patients with MEN 2B who have MTC are more likely than those with MEN 2A (or familial MTC) to have locally aggressive disease. Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor; 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level; and 3) postoperative residual hypercalcitoninemia. 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. Codon analysis is useful for predicting prognosis. Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease. More than 95% of patients with MEN 2B have a mutation in exon 16 (codon 918), whereas 2% to 3% have a mutation in exon 15 (codon 883).

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). MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, 131I imaging cannot be used, and RAI treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, TSH suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levothyroxine dose.

Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease, because the possibility of MEN 2 should dictate testing for a 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 NCCN.org). Patients with pheochromocytomas must be treated preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery. Forced hydration and alpha-blockade are necessary to prevent hypotension after the tumor is removed. After institution of alpha-blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is 1 cm or larger or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is less than 1 cm and for unilateral thyroid disease (see Primary Treatment in the NCCN Guidelines for Medullary Thyroid Carcinoma). 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. Note that C634 mutations are the most common mutations. Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN 2B 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).

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. 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). Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development. A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with RET mutations for MEN 2A; longer follow-up is necessary to determine if these patients are cured. Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary. A bilateral central neck dissection (level VI) can be considered for all patients with MEN 2B. For those patients with MEN 2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if patients have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for these patients with primary tumor(s) 1 cm or larger in diameter (>0.5 cm for patients with MEN 2B) or for patients with central compartment lymph node metastases (see Primary Treatment in the NCCN Guidelines for Medullary Thyroid Carcinoma).

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

**Adjuvant RT**

EBRT and IMRT have not been adequately studied as adjuvant therapy in MTC. Slight improvements in local disease-free survival have been reported after EBRT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement. 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). EBRT or IMRT can also be given to palliate painful or progressing bone metastases.

**Persistently Increased Calcitonin**

Basal serum concentrations of calcitonin and CEA should be measured 2 or 3 months postoperatively. About 80% of patients with palpable MTC and 50% of those with nonpalpable but macroscopic MTC who undergo supposedly curative resection have serum calcitonin values indicative of residual disease. Those patients with residual disease may benefit from further evaluation to detect either residual resectable disease in the neck or the presence of distant metastases. Patients with detectable basal calcitonin or elevated CEA who have negative imaging and who are asymptomatic may be followed (see Surveillance in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Patients with a basal serum calcitonin value greater than 1000 pg/mL—and with no obvious MTC in the neck and upper mediastinum—probably have distant metastases, most likely in the liver. However, occasionally patients have relatively low serum CEA and calcitonin levels but have extensive metastatic disease; initial postoperative imaging is therefore reasonable despite the absence of very high serum markers.

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease, 15 patients with MEN 2A, and 6 patients with MEN 2B), the 5- and 10-year survival rates were 90% and 86%, respectively. 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. 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. 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. 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.

Postoperative Management and Surveillance

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

Patients with detectable serum markers (ie, calcitonin levels ≥150 pg/mL) should have contrast-enhanced CT (±PET) or MRI of the neck, chest, and abdomen with a liver protocol. Bone scan and MRI of axial skeleton should be considered in select patients such as those with very elevated calcitonin levels. 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.

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

Recurrent or Persistent Disease

Kinase inhibitors may be appropriate for select patients with recurrent or persistent MTC that is not resectable (see Recurrent or Persistent Disease in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Although kinase inhibitors may be recommended for patients with MTC, it is important to note that kinase inhibitors may not be appropriate for patients with stable or slowly progressive indolent disease.

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

Cabozantinib is a multitargeted kinase inhibitor that inhibits RET, VEGFR2, and MET. In a phase 3 randomized trial (EXAM) in patients with locally advanced or metastatic MTC (n = 330), cabozantinib increased median PFS when compared with placebo (11.2 vs. 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; \( P < .001 \)); overall survival data are not yet available. In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC. The NCCN Panel recommends cabozantinib (category 1) based on the phase III randomized trial and FDA approval (see Recurrent or Persistent Disease in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Rare adverse events with cabozantinib include severe bleeding and gastrointestinal perforations or fistulas; severe hemorrhage is a contraindication for cabozantinib.

When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended with (or without) postoperative EBRT or IMRT. For unresectable locoregional disease that is symptomatic or progressing by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, the following options can be considered: 1) EBRT or IMRT; 2) vandetanib (category 1); or 3) cabozantinib (category 1). Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include: 1) palliative resection, ablation (eg, radiofrequency, embolization), or other regional treatment; 2) vandetanib (category 1); or 3) cabozantinib (category 1) (see Recurrent or Persistent Disease in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but active surveillance is acceptable given the lack of data regarding alteration in outcome. The NCCN Panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone.

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

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

Novel therapies and the management of aggressive MTC have been reviewed. 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.\textsuperscript{461} A phase 2 trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with 131I.\textsuperscript{474} Overall survival was improved in the subset of patients with increased calcitonin doubling times.\textsuperscript{475}

### Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas (ATCs) are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.\textsuperscript{476} Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.\textsuperscript{477} Fewer than 10\% of patients are younger than age 50 years, and 60\% to 70\% of patients are women.\textsuperscript{126,477} The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.\textsuperscript{476,478} 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.\textsuperscript{7}

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.\textsuperscript{479} 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.\textsuperscript{478,480,481} Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, 131I imaging cannot be used and RAI treatment is not effective in these patients with ATC.\textsuperscript{478}

ATC is typically diagnosed based on clinical symptoms, unlike differentiated thyroid carcinoma, which is typically diagnosed after FNA on a suspicious thyroid nodule. Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner’s syndrome, stroke, and hoarseness due to vocal cord paralysis.\textsuperscript{482} Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15\% to 50\% of patients.\textsuperscript{402,483} The lungs and pleura are the most common site of distant metastases (≤90\% of patients with distant disease). About 5\% to 15\% of patients have bone metastases; 5\% have brain metastases; and a few have metastases to the skin, liver, kidneys, pancreas, heart, and adrenal glands.

### Diagnosis

The diagnosis of ATC is usually established by core or surgical biopsy. If FNA is suspicious or not definitive, core or surgical biopsy should be performed to establish the diagnosis of ATC.\textsuperscript{478} The appearance of ATCs varies widely; many ATCs have mixed morphologies. The most common morphology is biphasic spindle and giant cell tumor. Molecular techniques are not recommended for diagnosis of ATC.\textsuperscript{478} 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.\textsuperscript{112,478} Diagnostic procedures include a CBC with differential, comprehensive chemistry, TSH level, direct exam of larynx, and imaging studies. Neck ultrasound can rapidly assess tumor extension and invasion.\textsuperscript{482} 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.\textsuperscript{484} PET/CT scans from skull base to mid-thigh are recommended to accurately stage the patient. Bone metastases are usually lytic. Evaluation of vocal cord mobility can also be considered. All ATCs are considered stage IV (A, B, or C) (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma). The T4 category includes: T4a tumors that are intrathyroidal and T4b tumors that are extrathyroidal. Clinically apparent anaplastic tumors are usually unresectable.

**Prognosis**

No curative therapy exists for ATC; it is almost uniformly fatal.\textsuperscript{485,486} The median survival from diagnosis is about 5 months.\textsuperscript{478,487} The 1-year survival rate is about 20\%.\textsuperscript{483,487} 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.\textsuperscript{488} 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.\textsuperscript{489} Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, WBC count ≥10,000 mm\(^3\), and dyspnea as a presenting symptom.\textsuperscript{490,491}

**Treatment**

ATC has a very poor prognosis and responds poorly to conventional therapy. The role of palliative and supportive care is paramount and should be initiated early in the disease. At the outset of the diagnosis, it is critical that conversations about end-of-life care be initiated so that a clear understanding of how to manage the airway is undertaken, which is clear to the family and all providers. Tracheostomy is often a morbid and temporary treatment of the airway and may not be the option a patient would choose.\textsuperscript{488,492}

**Surgery**

Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.\textsuperscript{476} 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.\textsuperscript{488} If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with selective resection of all involved local or regional structures and nodes. Total thyroidectomy with attempted complete tumor resection has not been shown to prolong survival except for the few patients whose tumors are small and confined entirely to the thyroid or readily excised structures.\textsuperscript{487,489,493,494} Patients need to receive levothyroxine if total thyroidectomy is done.

**Radiation Therapy**

EBRT or IMRT can increase short-term survival in some patients; EBRT or IMRT can also improve local control and can be used for palliation (eg, to prevent asphyxiation).\textsuperscript{445,476,478,491,495-499} Surgical excision or external irradiation should be considered for isolated skeletal metastases. For solitary brain lesions, either neurosurgical resection or radiation therapy is recommended. Once brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months. Enteral nutrition may be useful for some patients who have difficulty swallowing (see Principles of Nutrition: Management and Supportive Care in the NCCN Guidelines for Head and Neck Cancer, available at NCCN.org). If enteral feeding is considered, a careful conversation should occur with the patient about their wishes.
Systemic Therapy

Treatment with single-drug chemotherapy is not very effective, although some patients may show disease response or have stable disease.\textsuperscript{478, 499} Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year.\textsuperscript{500} Distant metastases then become the leading cause of death.\textsuperscript{501} 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.\textsuperscript{499, 502-504} IMRT may be useful to reduce toxicity.\textsuperscript{445, 478, 505-509} However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival.

Systemic therapy recommendations are described in the algorithm (see Systemic Therapy for Anaplastic Thyroid Carcinoma in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).\textsuperscript{478, 510} Recommended regimens include paclitaxel and carboplatin combinations, docetaxel and doxorubicin combinations, paclitaxel alone, or doxorubicin alone.\textsuperscript{478, 511} 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.\textsuperscript{478} Chemotherapy alone can be considered for patients with unresectable or metastatic disease. Single-agent doxorubicin is the only agent that is approved by the FDA for ATC.\textsuperscript{478} Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease.\textsuperscript{512-514} If weekly paclitaxel is used, the ATA Guidelines recommend using paclitaxel at 60 to 90 mg/m\textsuperscript{2} IV weekly and not the dose previously reported in the study by Ain et al.\textsuperscript{478, 514}

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 fosfretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin [EPC2407], which are vascular disrupting agents), efatutazone (an oral PPAR gamma agonist), and novel multtargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.\textsuperscript{510, 515-522} Outside of clinical trials, targeted therapies are not currently recommended in the NCCN Guidelines for patients with ATC, although some are recommended for patients with papillary, follicular, Hürthle cell, or medullary carcinoma. A trial in 80 patients (FACT) reported that the addition of fosfretabulin—to a carboplatin/paclitaxel regimen—resulted in a nonsignificant increase in median survival (5.2 vs. 4.0 months).\textsuperscript{510, 523}

Multimodality therapy is recommended in patients with locally resectable disease (see Primary Treatment in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).\textsuperscript{478, 505, 510, 524-528} Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN Panel acknowledged that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported.\textsuperscript{529} 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.\textsuperscript{345-348} BRAF mutations have been reported in patients with ATC.\textsuperscript{482, 530-532}
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