



NCCN

National Comprehensive  
Cancer Network®

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# Thyroid Carcinoma

Version 2.2020 — July 15, 2020

[NCCN.org](https://www.NCCN.org)

[Continue](#)



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

\***Robert I. Haddad, MD/Chair †**  
Dana-Farber/Brigham and Women's  
Cancer Center

**Lindsay Bischoff, MD/Vice-Chair δ**  
Vanderbilt-Ingram Cancer Center

**Victor Bernet, MD δ**  
Mayo Clinic Cancer Center

**Erik Blomain, MD, PhD § ¥**  
Stanford Cancer Institute

**Naifa Lamki Busaidy, MD δ**  
The University of Texas  
MD Anderson Cancer Center

**Paxton Dickson, MD ¶**  
St. Jude Children's Research Hospital/The  
University of Tennessee Health Science Center

**Quan-Yang Duh, MD ¶**  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Hormoz Ehya, MD #**  
Fox Chase Cancer Center

**Whitney Goldner, MD δ**  
Fred & Pamela Buffett Cancer Center

**Megan Haymart, MD ¶ δ**  
University of Michigan Rogel Cancer Center

**Carl Hoh, MD φ**  
UC San Diego Moores Cancer Center

**Jason P. Hunt, MD ¶**  
Huntsman Cancer Institute  
at the University of Utah

**Andrei Iagaru, MD Φ**  
Stanford Cancer Institute

**Fouad Kandeel, MD, PhD δ**  
City of Hope National Medical Center

**Dominick M. Lamonica, MD ¶ φ**  
Roswell Park Comprehensive Cancer Center

**Stephanie Markovina, MD, PhD §**  
Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine

**Bryan McIver, MD, PhD δ**  
Moffitt Cancer Center

**Christopher D. Raeburn, MD ¶**  
University of Colorado Cancer Center

**Rod Rezaee, MD ¶ ζ**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer Center  
and Cleveland Clinic Taussig Cancer Institute

**John A. Ridge, MD, PhD ¶**  
Fox Chase Cancer Center

**Matthew D. Ringel, MD δ**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Mara Roth, MD δ**  
Fred Hutchinson Cancer Research Center/  
Seattle Cancer Care Alliance

**Randall P. Scheri, MD ¶**  
Duke Cancer Institute

**Jatin P. Shah, MD, PhD ¶**  
Memorial Sloan Kettering Cancer Center

**Jennifer A. Sipos, MD δ**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Rebecca Sippel, MD ¶**  
University of Wisconsin Carbone Cancer Center

**Robert C. Smallridge, MD δ**  
Mayo Clinic Cancer Center

**Cord Sturgeon, MD ¶**  
Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University

**Samuel Swisher-McClure, MD §**  
Abramson Cancer Center  
at the University of Pennsylvania

**Thomas N. Wang, MD, PhD ¶**  
O'Neal Comprehensive Cancer Center at UAB

**Lori J. Wirth, MD †**  
Massachusetts General Hospital  
Cancer Center

**Richard Wong, MD ¶**  
Memorial Sloan Kettering Cancer Center

**NCCN**  
**Susan Darlow, PhD**  
**Lisa A. Gurski, PhD**  
**Alyse Johnson-Chilla, MS**

δ Endocrinology  
¶ Internal medicine  
† Medical oncology  
Φ Nuclear medicine  
ζ Otolaryngology  
# Pathology  
¥ Patient Advocate

§ Radiation/Radiation  
oncology  
¶ Surgery/Surgical  
oncology  
\* Writing Committee  
Member

[NCCN Guidelines Panel Disclosures](#)

[Continue](#)



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

### [NCCN Thyroid Carcinoma Panel Members](#)

### [Summary of the Guidelines Updates](#)

#### Thyroid Carcinoma

##### [Nodule Evaluation \(THYR-1\)](#)

#### Papillary Carcinoma

##### [FNA Results, Diagnostic Procedures, Preoperative or Intraoperative Decision-Making Criteria, Primary Treatment \(PAP-1\)](#)

#### Follicular Carcinoma

##### [FNA Results, Diagnostic Procedures, Primary Treatment \(FOLL-1\)](#)

#### Hürthle Cell Carcinoma

##### [FNA Results, Diagnostic Procedures, Primary Treatment \(HÜRT-1\)](#)

#### Medullary Thyroid Carcinoma

##### [Clinical Presentation, Diagnostic Procedures, Primary Treatment \(MEDU-1\)](#)

##### [Germline Mutation of RET Proto-oncogene \(MEDU-3\)](#)

#### Anaplastic Carcinoma

##### [FNA or Core Biopsy Finding, Diagnostic Procedures, Establish Goals of Therapy, Stage \(ANAP-1\)](#)

##### [Systemic Therapy for Anaplastic Thyroid Carcinoma \(ANAP-A\)](#)

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

#### [Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma \(THYR-B\)](#)

#### [Principles of Radiation and Radioactive Iodine Therapy \(THYR-C\)](#)

#### [Staging](#)

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2020.

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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/member\\_institutions.aspx](#).

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

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).



Updates in Version 2.2020 of the NCCN Guidelines for Thyroid Carcinoma from Version 1.2020 include:

### Papillary Carcinoma

#### [PAP-10](#) (All changes also made on [FOLL-8](#) and [HÜRT-8](#))

- 2nd column, 2nd bullet: "and tumor mutational burden (TMB)" was added.
- "Pembrolizumab for patients with tumor mutational burden-high (TMB-H) ( $\geq 10$  mutations/megabase [mut/Mb]) tumors" was added as a systemic therapy option. Also for [PAP-11](#), [FOLL-9](#), and [HÜRT-9](#).

### Medullary Carcinoma

#### [MEDU-6](#) (All changes also made on [MEDU-7](#))

- "Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors" was added as a systemic therapy option (Useful in Certain Circumstances).
- "Genomic testing including tumor mutational burden (TMB) or..." was added to footnote s.

### Anaplastic Carcinoma

#### [ANAP-1](#)

- Footnote b was updated: "...BRAF, NTRK, ALK, and RET, and tumor mutational burden." Also for ANAP-2.

#### [ANAP-2](#)

- Reference for pembrolizumab for TMB-H was added to footnote g: "Marabelle A, et al. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019"

#### [ANAP-A \(2 of 3\)](#)

- "Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors" was added as a systemic therapy option (Useful in Certain Circumstances)

Updates in Version 1.2020 of the NCCN Guidelines for Thyroid Carcinoma from Version 2.2019 include:

### General

- Bethesda classification was added throughout the Guidelines.
- "Surveillance/Active surveillance" has been clarified throughout the Guidelines as "Nodule surveillance," "Monitoring of residual disease," "Active surveillance" or "Disease monitoring."
- "rhTSH" was replaced with "thyrotropin alfa" throughout the Guidelines.
- The [Principles of Radiation Therapy and Radioactive Iodine Therapy \(THYR-C\)](#) is new.
  - ▶ RAI recommendations and dosing have been moved to the new Principles page from the algorithm and footnotes.

### Thyroid Carcinoma

#### [THYR-1](#)

- Workup for Thyroid nodule(s) with normal or elevated TSH updated: "...sonographic features as described by the ATA and/or TI-RADS or Nodule surveillance." Also for THYR-4.
- Sonographic features table was replaced with a reference to the ATA and TI-RADS.
- Footnote b is new: "TI-RADS ([https://www.jacr.org/article/S1546-1440\(17\)30186-2/pdf](https://www.jacr.org/article/S1546-1440(17)30186-2/pdf)) or ATA (<https://www.ncbi.nlm.nih.gov/>)

[pmc/articles/PMC4739132/pdf/thy.2015.0020.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4739132/pdf/thy.2015.0020.pdf)" Also for THYR-2, THYR-3, and THYR-4.

#### [THYR-2](#)

- Benign (Bethesda II) Treatment updated: "Nodule surveillance as recommended by the ATA or TI-RADS If nodule growth, repeat FNA or consider surgery."
- Footnotes were removed:
  - ▶ Repeat ultrasound after 6–12 months, if stable for 1–2 years, then subsequent ultrasound can be considered at 3- to 5-year intervals.
  - ▶ Growth 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. Generally, more than two biopsies on a growing benign nodule are not indicated.

#### [THYR-3](#)

- Follicular or Hürthle cell neoplasm Treatment
  - ▶ 2nd bullet: "for follicular neoplasm" was removed.
  - ▶ 3rd bullet was updated: "Consider nodule surveillance if low risk or patient preference as recommended by the ATA or TI-RADS"

[Continued](#)

UPDATES



Updates in Version 1.2020 of the NCCN Guidelines for Thyroid Carcinoma from Version 2.2019 include:

**THYR-3** (continued)

- AUS/FLUS without radiographic suspicion of malignancy Treatment was updated
  - ▶ 2nd bullet: "(if Bethesda III on 2 or more occasions)" was added.
  - ▶ Last bullet was updated: "Consider nodule surveillance as recommended by the ATA or TI-RADS"
- Footnote g was updated: "Estimated risk of malignancy is 6%–18% without NIFTP and 10%–30% with NIFTP." Also for THYR-4.
- A footnote was deleted: "Molecular diagnostics may not perform well for Hürthle cell neoplasms." Also for THYR-4.

**Papillary Carcinoma**

**PAP-1**

- " $\geq 1$  cm and  $<1$  cm" bifurcation is new.
  - ▶  $<1$  cm pathway is new.
- $\geq 1$  cm Diagnostic Procedures were updated:
  - ▶ 2nd bullet: "CT/MRI with contrast for *locally advanced disease or vocal cord paresis fixed, bulky, or substernal lesions*."
  - ▶ Last bullet: "Strongly" was added.
- Preoperative or Intraoperative Decision-Making Criteria
  - ▶ Indications for total thyroidectomy (any present) 4th bullet was updated: "Cervical lymph node metastases *or gross central neck lymph node metastases*"
  - ▶ Indications for total thyroidectomy or lobectomy, if all criteria present last bullet was changed from "Tumor  $\leq 4$  cm..." to "Tumor 1–4 cm..."
  - ▶ Footnote b was updated: "Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in RAI treatment will not cause harm, although iodinated contrast will delay treatment with RAI." Also for FOLL-1 and HURT-1.
  - ▶ Footnote e is new: "Routine prophylactic central neck dissection is not indicated in most papillary thyroid cancers."

**PAP-2**

- Lobectomy + isthmusectomy, Any of the following:
  - ▶ "Gross" added to second bullet. Also for PAP-3.
  - ▶ 5th bullet is new: Confirmed contralateral disease"
  - ▶ 6th bullet updated: "Macroscopic Confirmed nodal metastasis"
  - ▶ Last bullet is new: "Poorly differentiated"

**PAP-2** (continued)

- Lobectomy + isthmusectomy, All of the following:
  - ▶ First bullet clarified: "Negative resection margins"
  - ▶ 3rd and 4th bullets were added to be consistent with PAP-3.
- Footnote g was updated: "Completion thyroidectomy is not required for *incidental* small volume pathologic N1a metastases (fewer than 3-  $<5$  involved nodes..."

**PAP-3**

- All of the following: "or NIFTP" was added to be consistent with PAP-2.

**PAP-4**

- This page was extensively revised. Also [FOLL-2](#) and [HÜRT-2](#).

**PAP-5**

- "Positive postoperative ultrasound, if done" was removed from RAI selectively recommended (if any present). (Also [FOLL-3](#) and [HÜRT-3](#))
- Considerations for Initial Postoperative Use of RAI After Total Thyroidectomy was updated: "RAI ablation is not required in patients with classic PTC who have T1b/T2 (1–4 cm) eN0–eN0a and/or eN0b disease or small-volume N1a disease (fewer than 3–5 metastatic lymph nodes with  $<5$   $<2$  mm of focus of cancer in node)..."

**PAP-6**

- This page was extensively revised. Also [FOLL-4](#) and [HÜRT-4](#).

**PAP-7** (All changes also made on [FOLL-5](#) and [HÜRT-5](#))

- 4th column:
  - ▶ "6 weeks following cross-sectional imaging: Consider 24-hour urine iodine." was added.
  - ▶ 2nd bullet: "(thyroid hormone withdrawal or rhTSH)" was removed.
- 5th column
  - ▶ "Confirmed radioiodine-avid tumor or *Thyroid remnant uptake only*" was updated.
  - ▶ "Cervical No uptake only" was updated.

**Continued**

**UPDATES**



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

Updates in Version 1.2020 of the NCCN Guidelines for Thyroid Carcinoma from Version 2.2019 include:

### PAP-8 (All changes also made on [FOLL-6](#) and [HÜRT-6](#))

- "Chest x-ray and PET/CT" was removed from Long-term disease monitoring for NED.
- Abnormal findings, Management, the following bullet was removed: "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)"
- The following footnote was removed: "If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH."

### PAP-9 (All changes also made on [FOLL-7](#) and [HÜRT-7](#))

- "and negative imaging" was added to the first bullet.
- 4th bullet was updated: "Stimulated Tg >10 ng/mL and rising Progressively rising Tg (basal or stimulated)"
- Locoregional recurrence
  - "Consider preoperative iodine total body scan" was added.
  - SBRT was added to EBRT option
  - "For select patients with limited burden nodal disease, consider..." was added to the last option.
- Metastatic disease
  - "RAI therapy for iodine-avid disease" was added.
  - "See PAP-10 if not amenable to RAI" was added.
  - Footnote ff was added to this page: "Ethanol ablation, cryoablation, RFA, etc."

### PAP-10 (All changes also made on [FOLL-8](#) and [HÜRT-8](#))

- 2nd column
  - 2nd bullet: "(including *NTRK* and *RET* gene fusions)" was added.
  - The last bullet is new: "Consider clinical trial"
- Last column (also for PAP-11, FOLL-9, and HÜRT-9)
  - 2nd sub bullet: Larotrectinib and entrectinib were moved to the algorithm from a footnote.
  - 3rd sub bullet is new: "Selplercatinib for patients with RET-fusion positive tumors."
  - The last bullet is new: "Best supportive care (See NCCN Guidelines for Palliative Care)".

### PAP-11 (All changes also made on [FOLL-9](#) and [HÜRT-9](#))

- Footnote mm is new: "RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease."
- Footnote oo is new: "TKI therapy should be used with caution in

otherwise untreated CNS metastases due to bleeding risk."

### Follicular Carcinoma

#### FOLL-1

- FNA Results: Follicular lesion of undetermined significance (FLUS) was removed.
- Diagnostic Procedures, 2nd bullet was updated: "CT/MRI with contrast for *locally advanced disease or vocal cord paresis fixed, bulky, or substernal lesions*." Also for [HÜRT-1](#).

#### FOLL-1 (continued)

- Pathways following Lobectomy/isthmusectomy were extensively revised. Also for [HÜRT-1](#).
- Footnote d was updated: "Minimally invasive *FTC* cancer is characterized as an *encapsulated tumor well-defined tumor* with microscopic capsular and/or a few foci of *without vascular invasion. (1–4) and often requires examination of at least 10 histologic sections to demonstrate*."

### Hürthle Cell Carcinoma

#### HÜRT-1

- "Molecular diagnostics may not perform well for Hürthle cell neoplasms." was removed from footnote a.
- Footnote d was updated: "Minimally invasive *HCC* cancer is characterized as an *encapsulated tumor well-defined tumor* with microscopic capsular and/or a few foci of *without vascular invasion. (1–4) and often requires examination of at least 10 histologic sections to demonstrate*."

#### HÜRT-3

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

### Medullary Carcinoma

#### MEDU-1

- Diagnostic Procedures, 9th bullet is new:
  - First sub bullet was updated: "Consider contrast-enhanced CT of neck/chest and liver MRI..."

[Continued](#)

**UPDATES**



Updates in Version 1.2020 of the NCCN Guidelines for Thyroid Carcinoma from Version 2.2019 include:

- Footnote f was updated: "*Imaging may be indicated based on high burden of disease, Liver imaging is seldom needed if calcitonin < 400 pg/mL, or elevated CEA levels.*"

### MEDU-2

- Genetic counseling was moved to the 3rd bullet and updated: "*Consider with genetic counseling*"
- Footnote g was updated: "...additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) *may not be necessary is generally unnecessary unless...*"
- Footnote h is new: "Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor."

### MEDU-3

- "Neck CT with contrast" was added to Additional Workup for MEN2B and MEN2A/FMTC.

### MEDU-5

- Detectable basal calcitonin or Elevated CEA
  - "FDG PET/CT or Ga-68 DOTATATE or MRI with contrast of the neck, chest, abdomen with liver protocol" was moved from the 3rd column to "Disease monitoring" column.
  - Last bullet
    - ◊ "Consider" was added.
    - ◊ Imaging recommendations were moved from a footnote into this bullet.

### MEDU-6 (changes also made on MEDU-7)

- Selercatinib (*RET mutation-positive*) was added as a preferred treatment option.
- Footnote s is new: *RET somatic genotyping in patients who are germline wild-type or germline unknown.*
- Footnote q was updated: "...are not an indication for treatment with *systemic therapy vandetanib or cabozantinib.*"

### MEDU-7

- Footnote w: "vandetanib or cabozantinib" was replaced with "preferred systemic therapy options".

### Anaplastic Carcinoma

#### ANAP-1

- "Molecular testing for actionable mutations" was added to Diagnostic Procedures
  - Footnote b is new: "Molecular testing should include BRAF, NTRK, ALK, and RET."
- Establish Goals of Therapy, first bullet: "Expedient" was added
- "Resectable" and "Unresectable" bifurcation is new. The following pathways were extensively revised.

#### ANAP-2

- Aggressive therapy Treatment, 3rd bullet: "if not previously done" was added.
- "Consider selercatinib if *RET-fusion positive*" with reference was added to footnote g.

#### ANAP-A (2 of 3)

- Entrectinib was moved from Other Recommended Regimens to Preferred Regimens.
- Selercatinib (*RET-fusion positive*) was added as a preferred regimen with dosing and reference.
- Reference number 4 was updated to the published manuscript.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### CLINICAL PRESENTATION

### WORKUP

### FNA RESULTS

For thyroid nodule known or suspected on exam or incidental imaging finding:

- Measure thyroid-stimulating hormone (TSH)
- Ultrasound of thyroid and neck including lateral neck lymph node compartments

Thyroid nodule(s) with low TSH

Radioiodine imaging iodine-123 thyroid uptake and scan

Autonomously functioning (hot)

Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)<sup>c</sup>

Thyroid nodule(s) with normal or elevated TSH<sup>a</sup>

Hypofunctional

Consider ultrasound-guided FNA based on clinical and sonographic features as described by the ATA and/or TI-RADS<sup>b</sup> or Nodule surveillance<sup>c</sup>

Thyroid lymphoma or Insufficient biopsy, nondiagnostic (Bethesda I) or Benign (Bethesda II)

See [THYR-2](#)

Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS) (Bethesda III) or Follicular or Hürthle cell neoplasm (Bethesda IV)

See [THYR-3](#) and [THYR-4](#)

Carcinoma or suspicious for carcinoma (Bethesda V and VI)

See [THYR-3](#)

<sup>a</sup> Evaluate and treat for hypothyroidism as clinically indicated.

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

<sup>c</sup> For well-defined, autonomous nodules FNA is rarely indicated and repeat ultrasound may not be necessary. For other 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. If growth and/or change in ultrasonographic features, consider FNA and follow [THYR-2](#), [THYR-3](#), and [THYR-4](#) for subsequent management.

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Cibas ES and Ali SZ. Thyroid 2017;27(11):1341-1346. <https://www.ncbi.nlm.nih.gov/pubmed/29091573>. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

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

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



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

### FNA RESULTS

### TREATMENT

Thyroid  
lymphoma

[See NCCN Guidelines for B-Cell Lymphomas](#)

Insufficient biopsy,  
nondiagnostic  
(Bethesda I)

Cystic

Correlate with ultrasound, re-aspirate suspicious areas

Solid

Repeat FNA with ultrasound guidance and immediate  
cytologic review for adequacy of specimen (preferred)  
or  
Consider surgery if repeat non-diagnostic FNAs

Benign<sup>d</sup>  
(Bethesda II)

Nodule surveillance as recommended by the ATA or TI-RADS<sup>b</sup>

Diagnostic categories for FNA results reflect NCI state of the science conference,  
the Bethesda Classification. Cibas ES and Ali SZ. Thyroid 2017;27(11):1341-1346.  
<https://www.ncbi.nlm.nih.gov/pubmed/29091573>. Cytology reports should be  
interpreted in light of terminology used by local cytopathologists.

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

<sup>d</sup>Includes nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, and Hashimoto's thyroiditis. Estimated risk of malignancy is approximately 5% or less;  
consider nodule surveillance.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### FNA RESULTS

Carcinoma or suspicious for carcinoma (Bethesda V and VI)

Papillary or suspicious for papillary

### TREATMENT<sup>i</sup>

[See Primary Treatment \(PAP-1\)](#)

Medullary or suspicious for medullary

[See Primary Treatment \(MEDU-1\)](#)

Anaplastic or suspicious for anaplastic

[See Primary Treatment \(ANAP-1\)](#)

Follicular or Hürthle cell neoplasm<sup>e,f</sup> (Bethesda IV)

High clinical and/or radiographic suspicion of malignancy<sup>h</sup>

Yes → Consider lobectomy or total thyroidectomy<sup>j</sup> for definitive diagnosis/treatment

[See PAP-1](#)  
[See FOLL-1](#)  
[See HÜRT-1](#)

- No →
- Consider diagnostic lobectomy
  - Consider molecular diagnostics<sup>f</sup> ([See THYR-4](#))
  - Consider nodule surveillance if low risk or patient preference as recommended by the ATA or TI-RADS<sup>b</sup>

Atypia of undetermined significance/Follicular lesion of undetermined significance<sup>f,g</sup> (AUS/FLUS) (Bethesda III)

High clinical and/or radiographic suspicion of malignancy<sup>h</sup>

Yes → Consider lobectomy or total thyroidectomy<sup>j</sup> for definitive diagnosis/treatment

[See PAP-1](#)  
[See FOLL-1](#)  
[See HÜRT-1](#)

- No →
- Repeat FNA<sup>k</sup>
  - Consider diagnostic lobectomy (if Bethesda III on 2 or more occasions)
  - Consider molecular diagnostics<sup>f</sup> ([See THYR-4](#))
  - Consider nodule surveillance as recommended by the ATA or TI-RADS<sup>b</sup>

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

<sup>e</sup> Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 15%–40%. Numbers may vary by institution or cytopathologist.

<sup>f</sup> 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 nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.

<sup>g</sup> Estimated risk of malignancy is 6%–18% without NIFTP and 10%–30% with NIFTP.

<sup>h</sup> Based on rapid growth of nodule, imaging, physical exam, age, clinical history of radiation, and family history.

<sup>i</sup> The order of the treatment options does not indicate preference.

<sup>j</sup> Total thyroidectomy may be considered for Hürthle cell neoplasm (Bethesda IV), history of radiation exposure, or contralateral lobe lesions.

<sup>k</sup> Consider second opinion pathology.

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Cibas ES and Ali SZ. Thyroid 2017;27(11):1341-1346. <https://www.ncbi.nlm.nih.gov/pubmed/29091573>.

Cytology reports should be interpreted in light of terminology used by local cytopathologists.

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

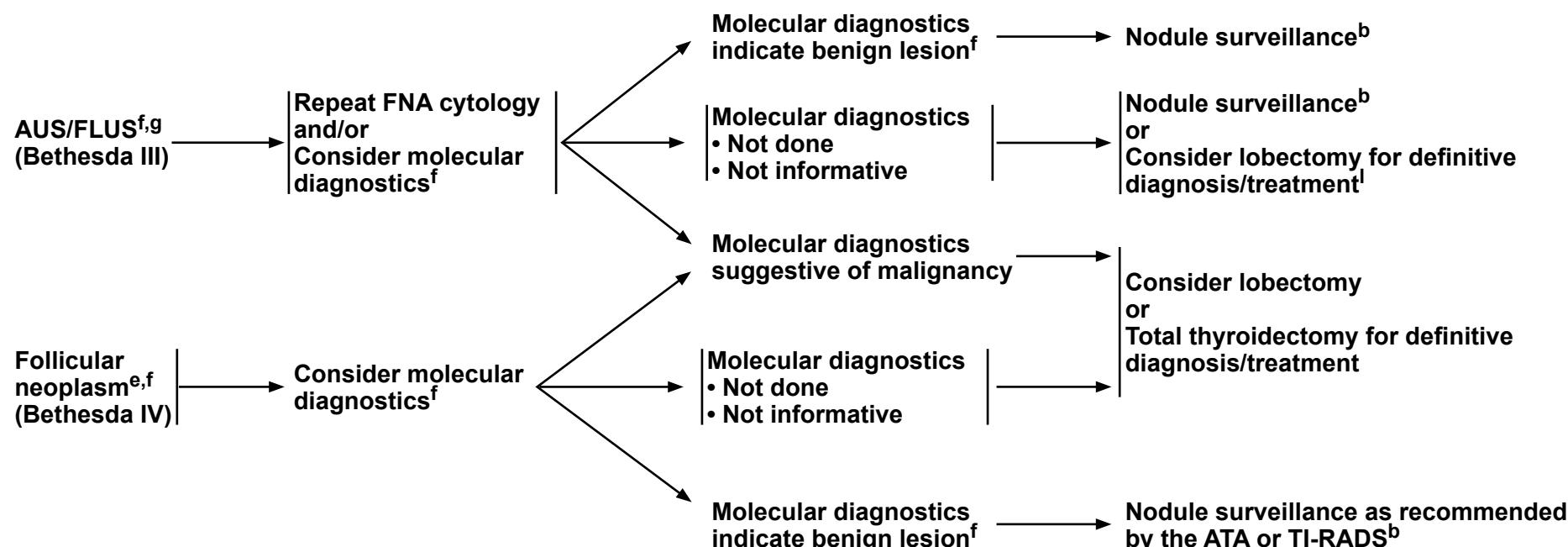
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### MOLECULAR DIAGNOSTIC RESULTS



Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Cibas ES and Ali SZ. Thyroid 2017;27(11):1341-1346. <https://www.ncbi.nlm.nih.gov/pubmed/29091573>. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

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

<sup>e</sup> Alternative term: Suspicious for follicular neoplasm. Estimated risk of malignancy is 15%–40%. Numbers may vary by institution or cytopathologist.

<sup>f</sup> The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, AUS, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see PAP-1. If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.

<sup>g</sup> Estimated risk of malignancy is 6%–18% without NIFTP and 10%–30% with NIFTP.

<sup>l</sup> Clinical risk factors, sonographic patterns, and patient preference can help determine whether nodule surveillance or lobectomy is appropriate.

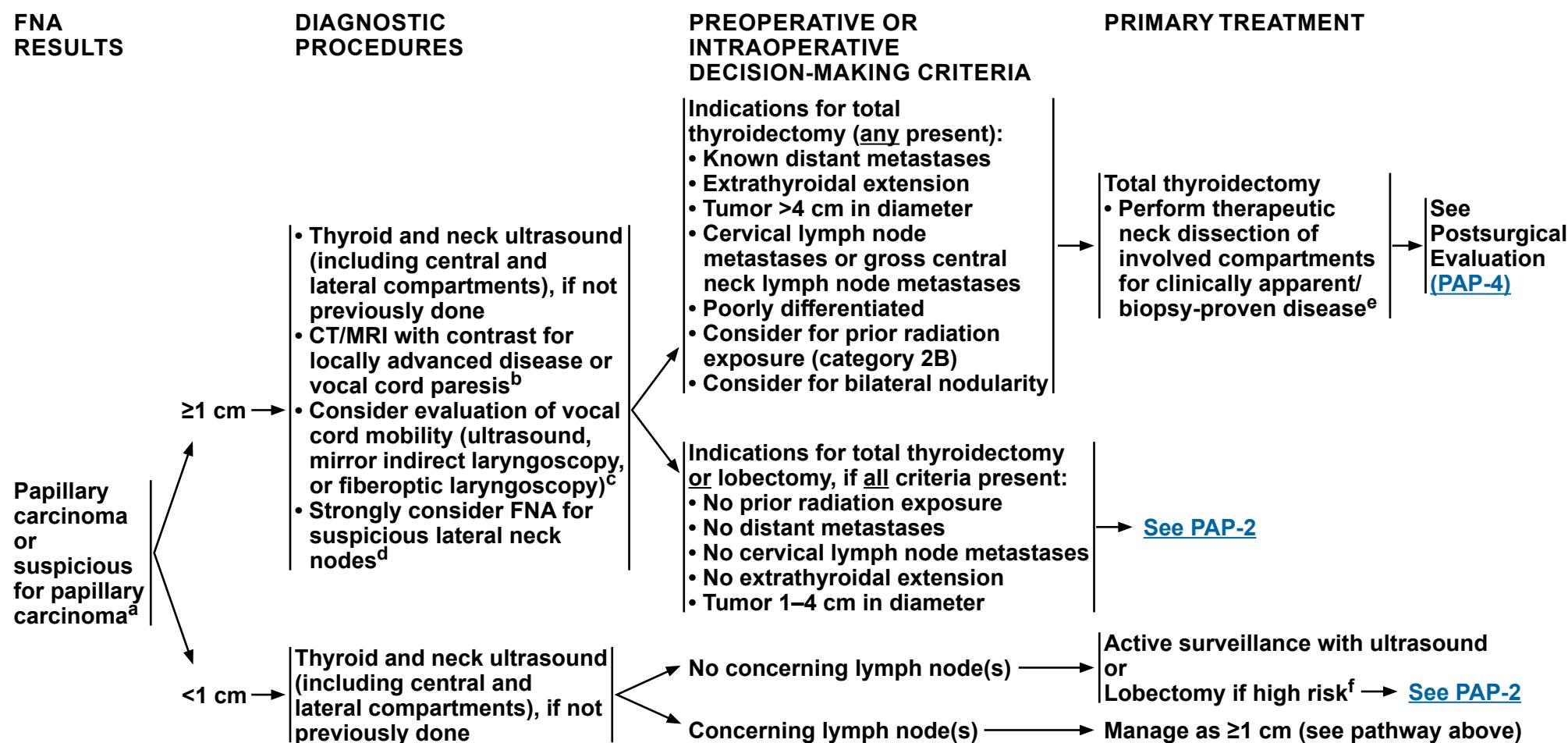
Note: All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma



<sup>a</sup> There is a potential role for lobectomy with or without frozen section if FNA is suspicious but not diagnostic for papillary carcinoma.

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

<sup>c</sup> 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.

<sup>d</sup> Tg washout is useful in diagnosis of lymph node metastases and recommended if cytology is negative.

<sup>e</sup> Routine prophylactic central neck dissection is not indicated in most papillary thyroid cancers.

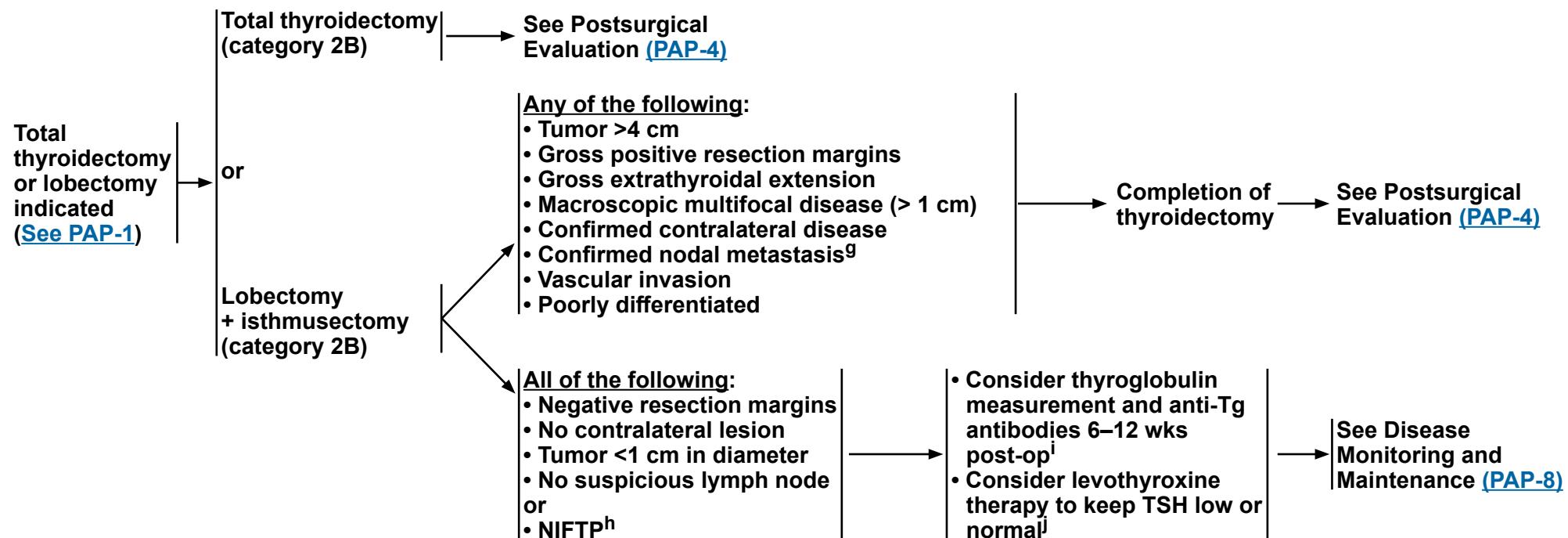
<sup>f</sup> Posterior location, abutting the trachea or apparent invasion, etc.

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

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



**PRIMARY TREATMENT**



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

<sup>h</sup> 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. Ongoing surveillance is recommended.

<sup>i</sup> May be useful for obtaining a postoperative baseline.

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

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

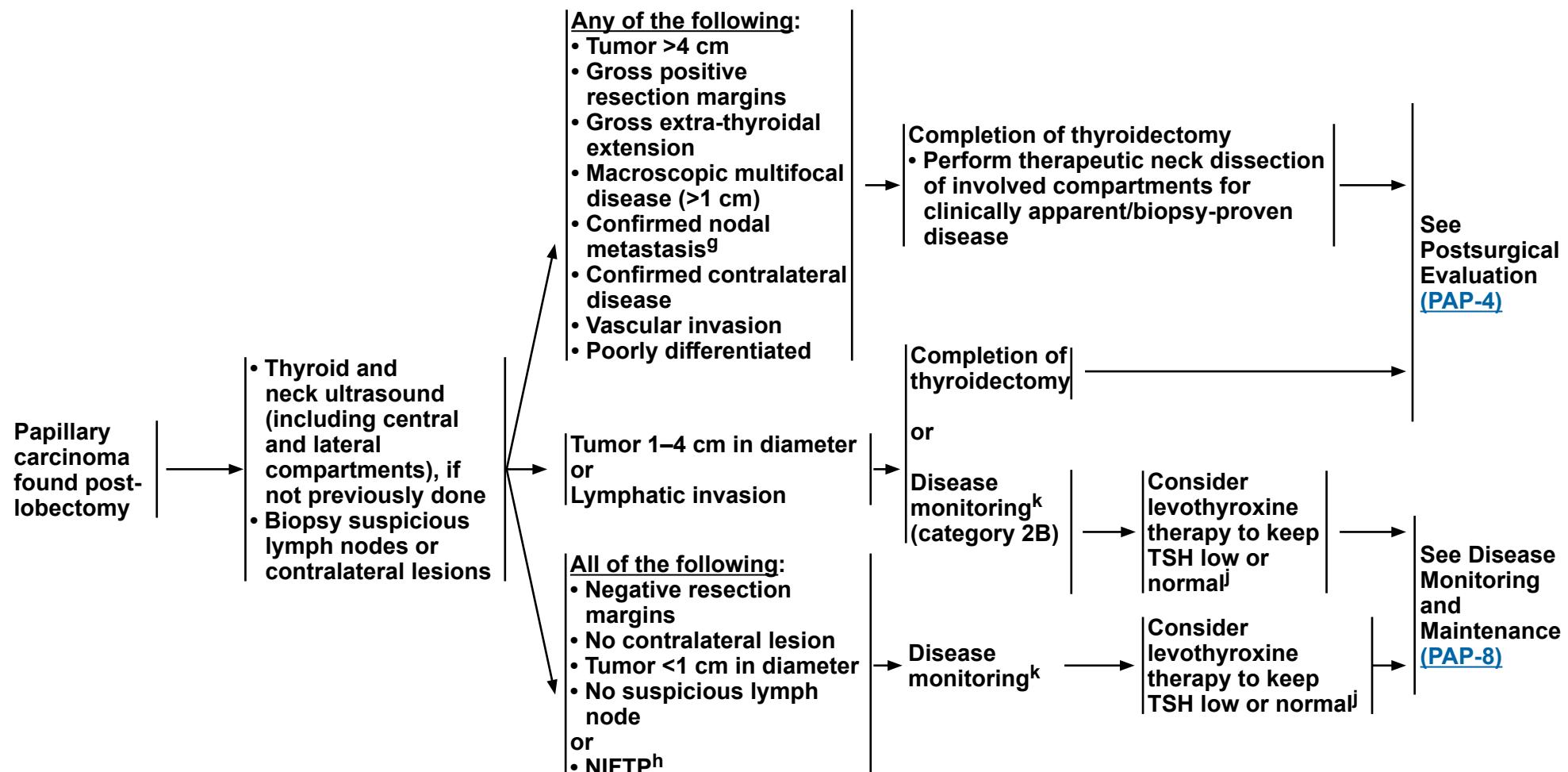
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

### CLINICAL PRESENTATION



<sup>g</sup> Completion of thyroidectomy is not required for incidental small volume pathologic N1A metastases (<5 involved nodes with no metastasis >5 mm in largest dimension). [See PAP-5](#).

<sup>h</sup> 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. Ongoing surveillance is recommended.

<sup>j</sup> [See Principles of TSH Suppression \(THYR-A\)](#).

<sup>k</sup> Measurement of thyroglobulin and antithyroglobulin antibodies may be useful for obtaining a postoperative baseline.

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

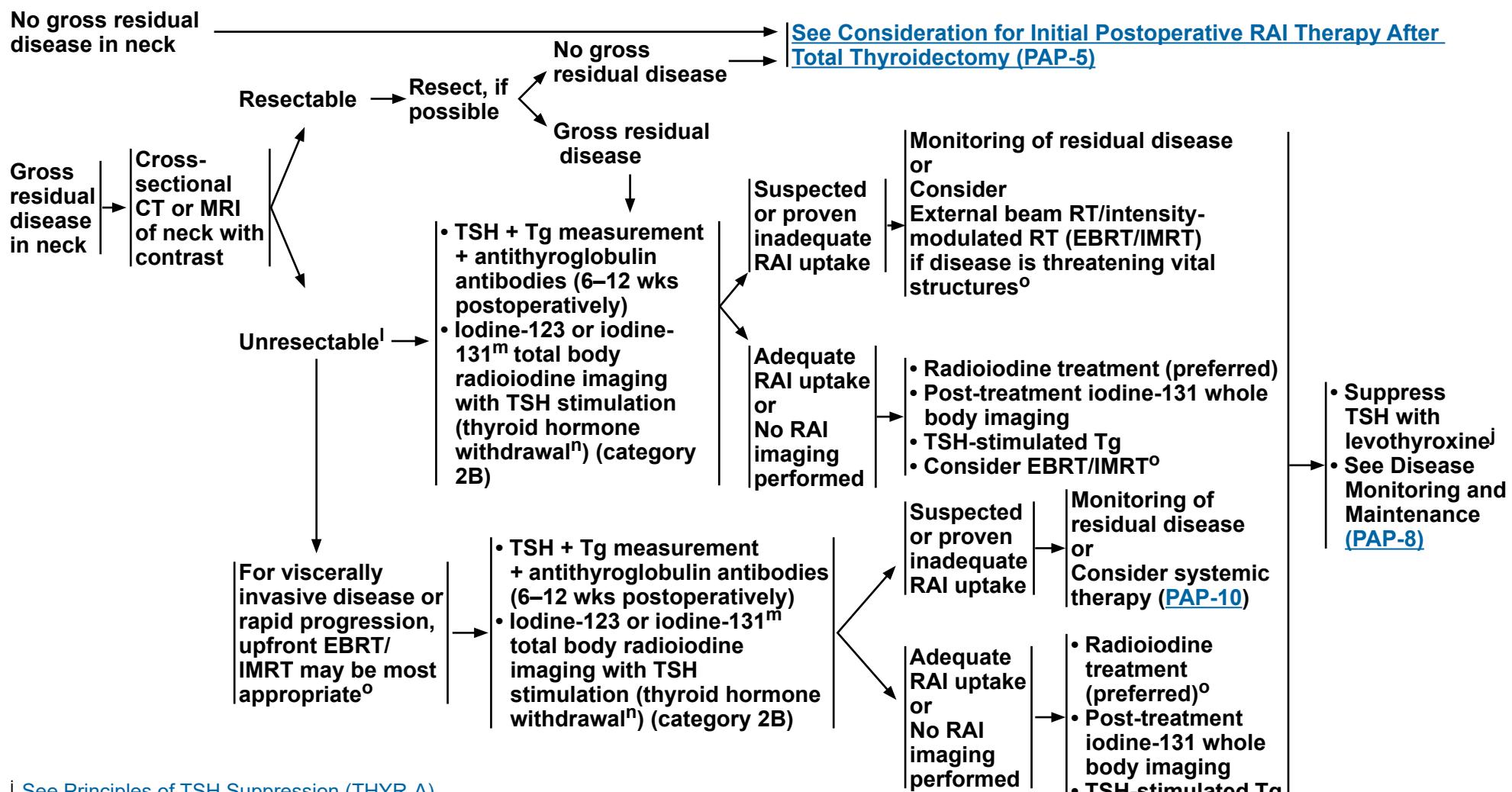
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

### POSTSURGICAL EVALUATION



<sup>j</sup> [See Principles of TSH Suppression \(THYR-A\).](#)

<sup>l</sup> For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.

<sup>m</sup> If considering dosimetry iodine-131 is the preferred agent.

<sup>n</sup> For contraindications to withdrawal, thyrotropin alfa may be used.

<sup>o</sup> [See Principles of Radiation and RAI Therapy \(THYR-C\).](#)

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

### CLINICOPATHOLOGIC FACTORS

RAI not typically recommended (if all present):

- Classic papillary thyroid carcinoma (PTC)
- Largest primary tumor <2 cm
- Intrathyroidal
- Unifocal or multifocal (all foci ≤1 cm)
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL<sup>p</sup>
- Negative postoperative ultrasound, if done<sup>q</sup>

RAI selectively recommended (if any present):

- Largest primary tumor 2–4 cm
- High-risk histology<sup>r</sup>
- Lymphatic invasion
- Cervical lymph node metastases
- Macroscopic multifocality (one focus >1 cm)
- Postoperative unstimulated Tg <5–10 ng/mL<sup>p</sup>
- Microscopic positive margins

RAI typically recommended (if any present):

- Gross extrathyroidal extension
- Primary tumor >4 cm
- Postoperative unstimulated Tg >5–10 ng/mL<sup>p,s</sup>
- Bulky or >5 positive lymph nodes

Known or suspected distant metastases at presentation

Gross residual disease not amenable to RAI therapy

### CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

RAI ablation is not required in patients with classic PTC who have T1b/T2 (1–4 cm) N0a and/or N0b disease or small-volume N1a disease (fewer than 5 metastatic lymph nodes with <2 mm of focus of cancer in node), particularly if the postoperative Tg is <1 ng/mL in the absence of interfering anti-Tg antibodies.

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

RAI not typically indicated,  
[See PAP-8](#)

RAI being considered,  
[See PAP-6](#)

Amenable to RAI  
[See PAP-7](#)

[See PAP-10](#)

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

<sup>q</sup> If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.

<sup>r</sup> ie, poorly differentiated, tall cell, columnar cell, and hobnail variants.

<sup>s</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.

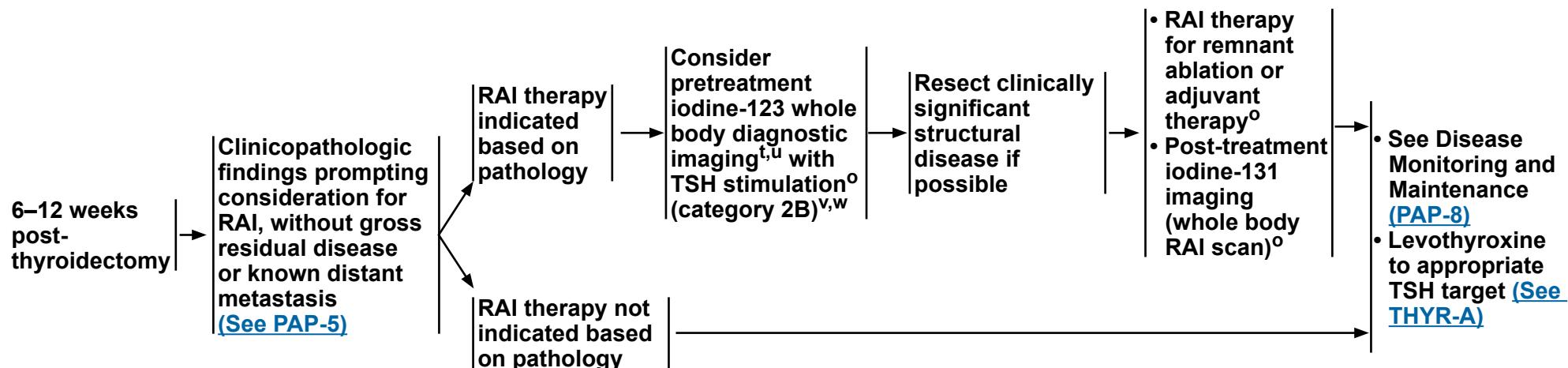
For general principles related to radioactive iodine (RAI) therapy, see the [Principles of Radiation and Radioactive Iodine Therapy \(THYR-C\)](#).

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

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



**RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES**



<sup>o</sup>See Principles of Radiation and RAI Therapy (THYR-C).

<sup>t</sup>Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

<sup>u</sup>A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.

<sup>v</sup>Alternatively, low-dose iodine-131 (1–3 mCi) may be used.

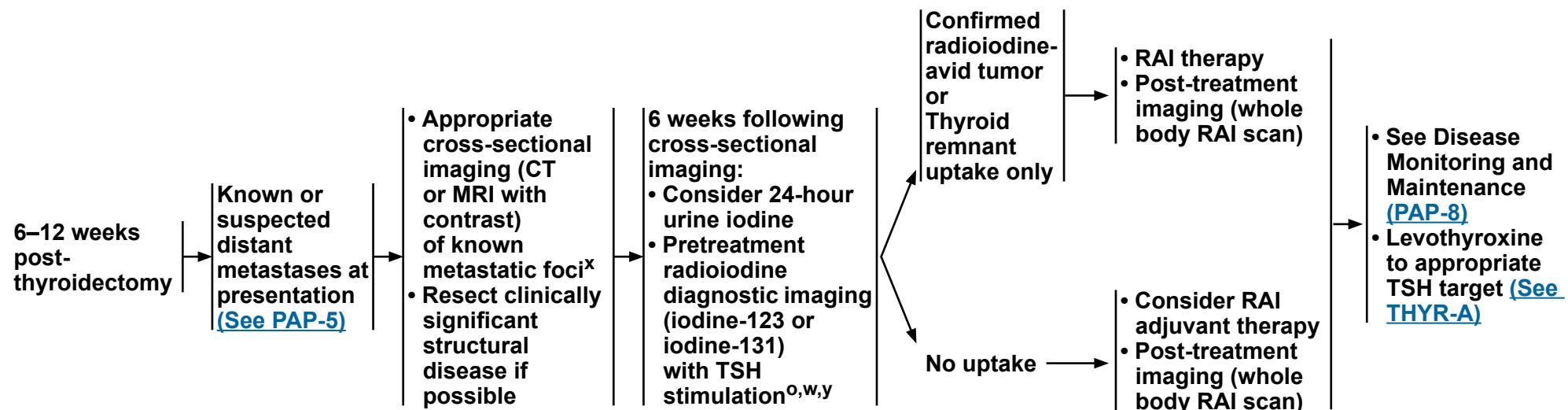
<sup>w</sup>While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry 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 glomerular filtration rate (GFR). Dialysis patients require special handling.

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

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



**KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE**



<sup>o</sup>See Principles of Radiation and RAI Therapy (THYR-C).

<sup>w</sup>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.

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

<sup>y</sup>Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

### DISEASE MONITORING AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound<sup>z</sup>
- 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<sup>aa</sup>
- Consider TSH-stimulated radioiodine whole body imaging in high-risk patients, patients with previous RAI-avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance

### FINDINGS

No evidence of disease (NED)

Abnormal findings

### MANAGEMENT

#### Long-term disease monitoring<sup>bb</sup>

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

→ Recurrent disease ([See PAP-9](#))

#### Additional workup

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

→ Recurrent disease ([See PAP-9](#)) or Metastatic disease ([See PAP-10](#))

<sup>z</sup> A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

<sup>aa</sup> 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.

<sup>bb</sup> [See NCCN Guidelines for Survivorship.](#)

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

### RECURRENT DISEASE

- Stimulated Tg 1–10 ng/mL and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive<sup>cc</sup>

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

Locoregional recurrence

Metastatic disease

<sup>j</sup> [See Principles of TSH Suppression \(THYR-A\).](#)

<sup>o</sup> [See Principles of Radiation and RAI Therapy \(THYR-C\).](#)

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

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

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

<sup>dd</sup> The administered activity of RAI therapy should be adjusted for pediatric patients. [See Principles of Radiation and RAI Therapy \(THYR-C\).](#)

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

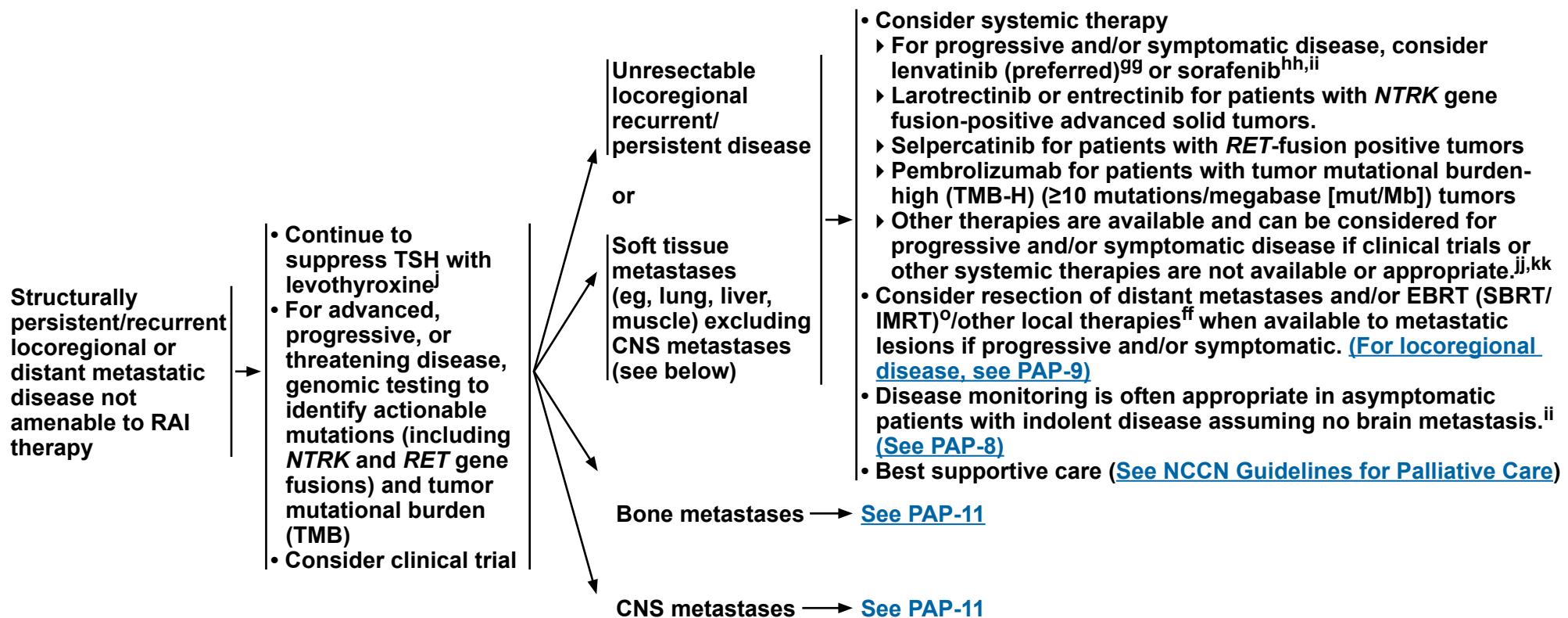
<sup>ff</sup> Ethanol ablation, cryoablation, RFA, etc.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

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



<sup>j</sup> [See Principles of TSH Suppression \(THYR-A\)](#).

<sup>o</sup> [See Principles of Radiation and RAI Therapy \(THYR-C\)](#).

<sup>ff</sup> Ethanol ablation, cryoablation, RFA, etc.

<sup>gg</sup> In a subset of patients (older than 65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.

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

<sup>ii</sup> Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. [See Principles of Kinase Inhibitor Therapy \(THYR-B\)](#).

<sup>jj</sup> Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

<sup>kk</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Papillary Carcinoma

### TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY<sup>mm</sup>

Bone metastases →

- Consider surgical palliation and/or EBRT/SBRT/other local therapies<sup>ff</sup> 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.<sup>ii</sup>
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease.<sup>ii</sup> ([See PAP-8](#))
- Consider systemic therapy
  - ▶ For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.<sup>hh</sup>
  - ▶ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - ▶ Selpercatinib for patients with *RET*-fusion positive tumors
  - ▶ Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors
  - ▶ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.<sup>ii,jj,kk</sup>
- Best supportive care ([See NCCN Guidelines for Palliative Care](#))

CNS metastases →

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred or
- For multiple CNS lesions, consider radiotherapy, including image-guided radiotherapy, and/or resection in select cases and/or
- Consider systemic therapy
  - ▶ For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib<sup>hh,nn,oo</sup> and/or
  - ▶ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - ▶ Selpercatinib for patients with *RET*-fusion positive tumors
  - ▶ Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors and/or
  - ▶ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.<sup>ii,jj,kk,nn</sup>
- Best supportive care ([See NCCN Guidelines for Palliative Care](#))

<sup>ff</sup> Ethanol ablation, cryoablation, RFA, etc.

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

<sup>ii</sup> Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. [See Principles of Kinase Inhibitor Therapy \(THYR-B\)](#).

<sup>jj</sup> Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

<sup>kk</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

<sup>ii</sup> Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia.

<sup>mm</sup> RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

<sup>nn</sup> After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.

<sup>oo</sup> TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

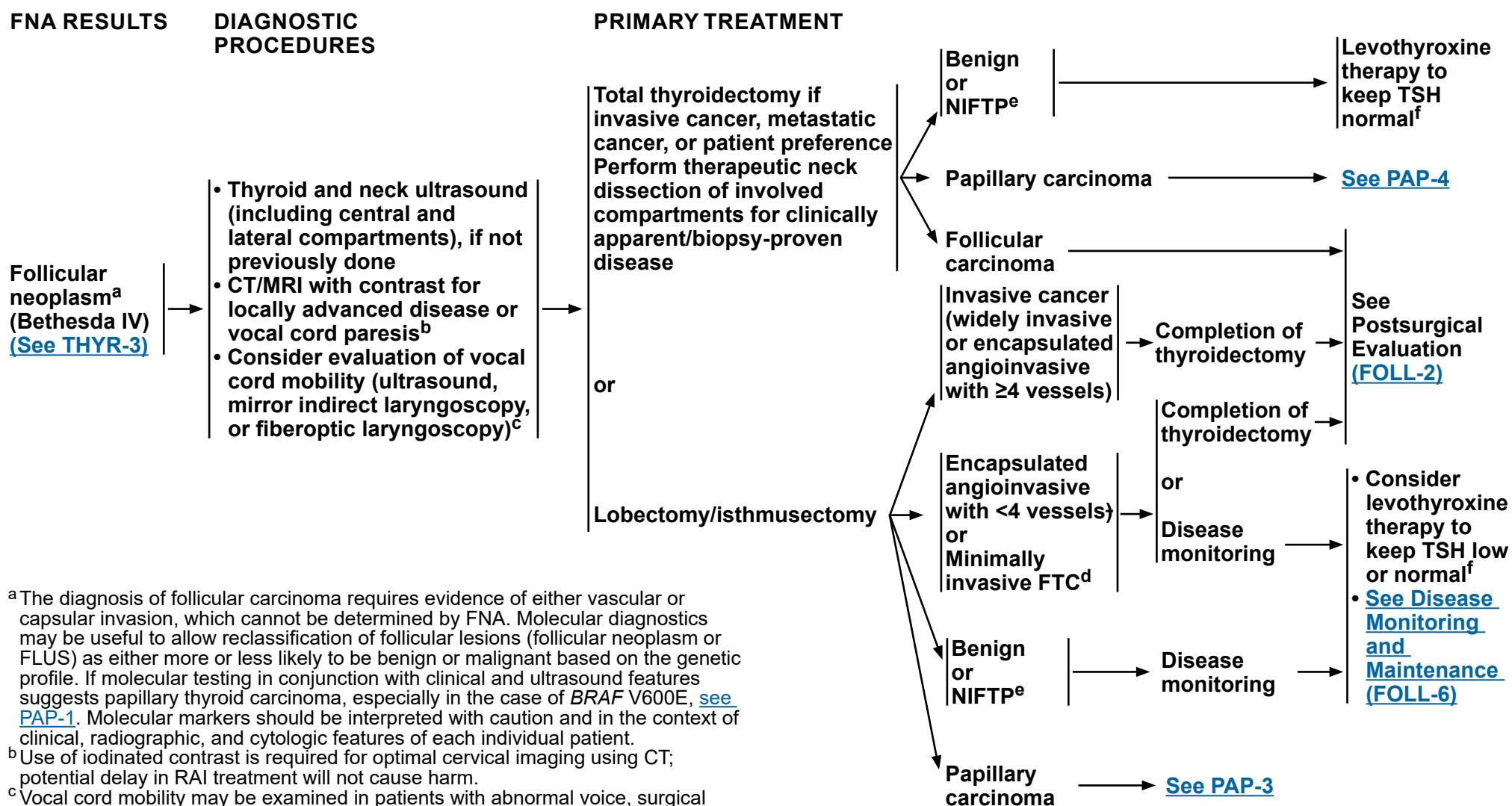
Note: All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma



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

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

<sup>c</sup>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.

<sup>d</sup>Minimally invasive follicular thyroid carcinoma (FTC) is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

<sup>e</sup>Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with NIFTP has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.

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

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

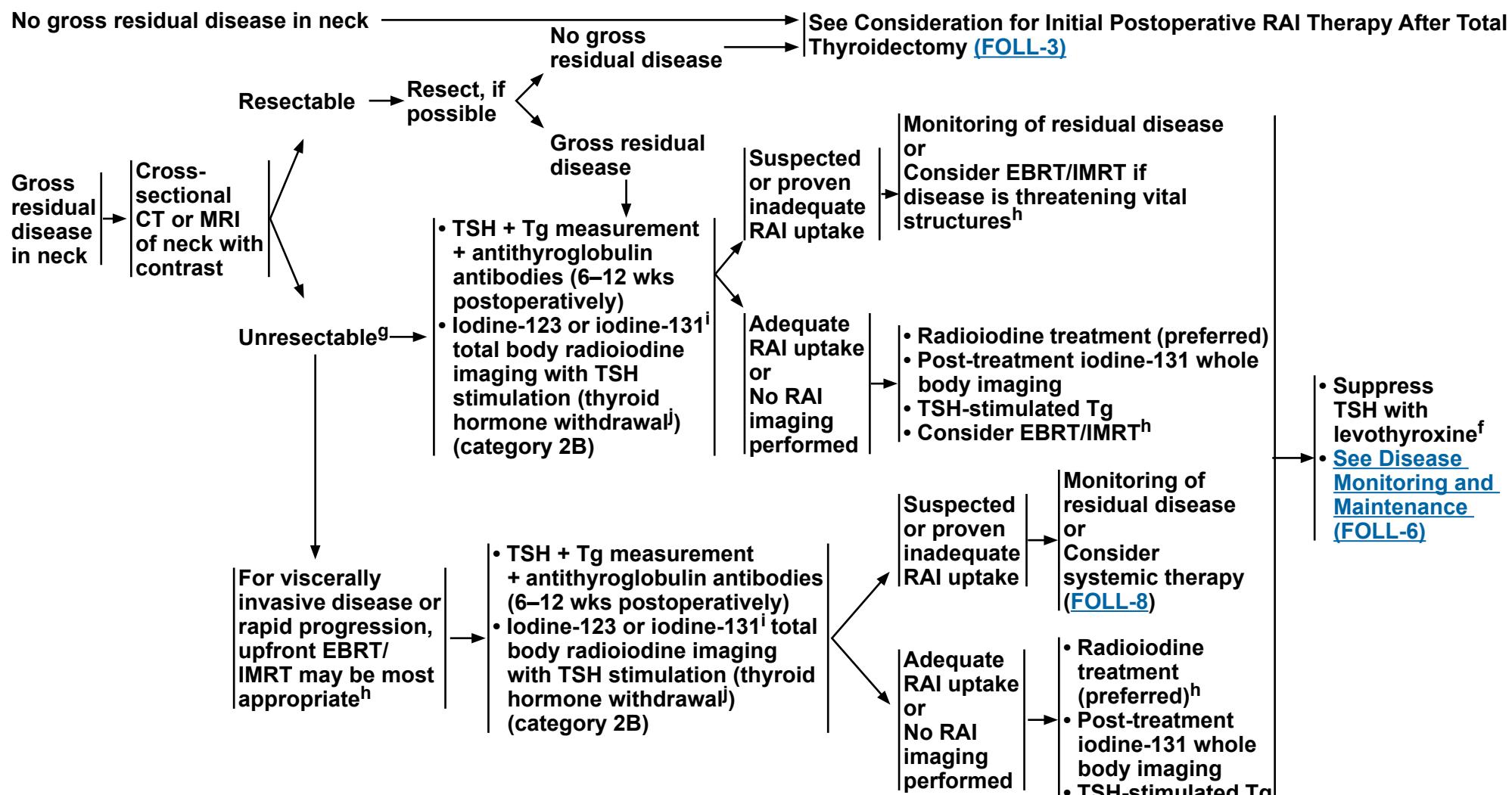
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

### POSTSURGICAL EVALUATION



<sup>f</sup> [See Principles of TSH Suppression \(THYR-A\).](#)

<sup>g</sup> For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.

<sup>h</sup> [See Principles of Radiation and RAI Therapy \(THYR-C\).](#)

<sup>i</sup> If considering dosimetry iodine-131 is the preferred agent.

<sup>j</sup> For contraindications to withdrawal, thyrotropin alfa may be used.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

### CLINICOPATHOLOGIC FACTORS

RAI not typically recommended (if all present):

- Largest primary tumor <2 cm
- Intrathyroidal
- No vascular invasion
- Clinical N0
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL<sup>k</sup>
- Negative postoperative ultrasound, if done<sup>l</sup>

RAI selectively recommended (if any present):

- Largest primary tumor 2–4 cm
- Minor vascular invasion<sup>d</sup>
- Cervical lymph node metastases
- Postoperative unstimulated Tg <5–10 ng/mL<sup>k</sup>
- Microscopic positive margins

RAI recommended (if any present):

- Gross extrathyroidal extension
- Primary tumor >4 cm
- Extensive vascular invasion<sup>d</sup>
- Postoperative unstimulated Tg >5–10 ng/L<sup>k,m</sup>
- Bulky or >5 positive lymph nodes

Known or suspected distant metastases at presentation

Gross residual disease not amenable to RAI therapy

### CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

RAI not typically indicated  
(See Surveillance FOLL-6)

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

RAI being considered,  
see FOLL-4

Amenable to RAI  
(See FOLL-5)

See FOLL-8

<sup>d</sup> Minimally invasive follicular thyroid carcinoma (FTC) is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

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

<sup>l</sup> If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.

<sup>m</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.

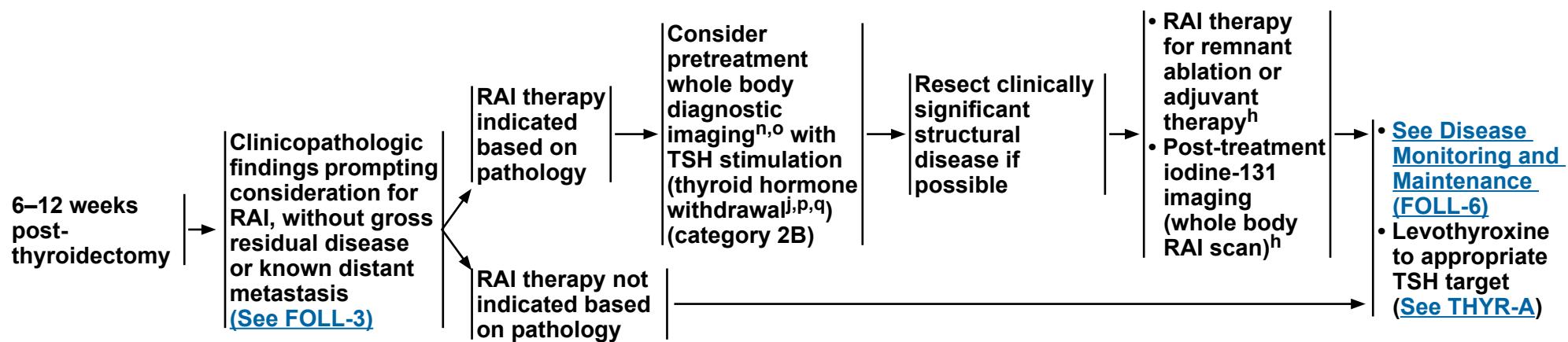
For general principles related to RAI therapy, see the [Principles of Radiation and Radioactive Iodine Therapy \(THYR-C\)](#)

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

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



**RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES**



<sup>h</sup> See Principles of Radiation and RAI Therapy (THYR-C).

<sup>j</sup> For contraindications to withdrawal, thyrotropin alfa may be used.

<sup>n</sup> Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

<sup>o</sup> A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.

<sup>p</sup> Alternatively, low-dose iodine-131 (1–3 mCi) may be used.

<sup>q</sup> 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.

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

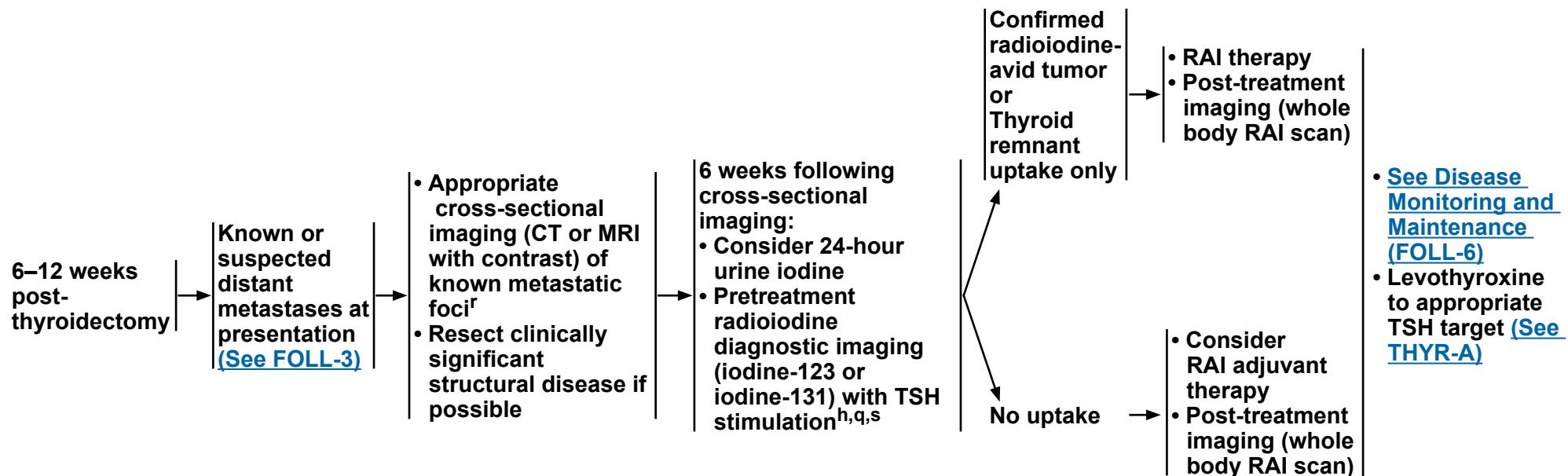
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

### KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE



<sup>h</sup> See Principles of Radiation and RAI Therapy (THYR-C).

<sup>q</sup> 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.

<sup>r</sup> 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.

<sup>s</sup> Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

### DISEASE MONITORING AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound<sup>t</sup>
- 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<sup>u</sup>
- Consider TSH-stimulated radioiodine whole body imaging in high-risk patients, patients with previous RAI-avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance

### FINDINGS MANAGEMENT

NED →

Abnormal findings →

#### Long-term disease monitoring<sup>v</sup>

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

Recurrent disease  
(See FOLL-7)

#### Additional workup

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

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

<sup>t</sup> A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

<sup>u</sup> 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.

<sup>v</sup> See NCCN Guidelines for Survivorship.

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

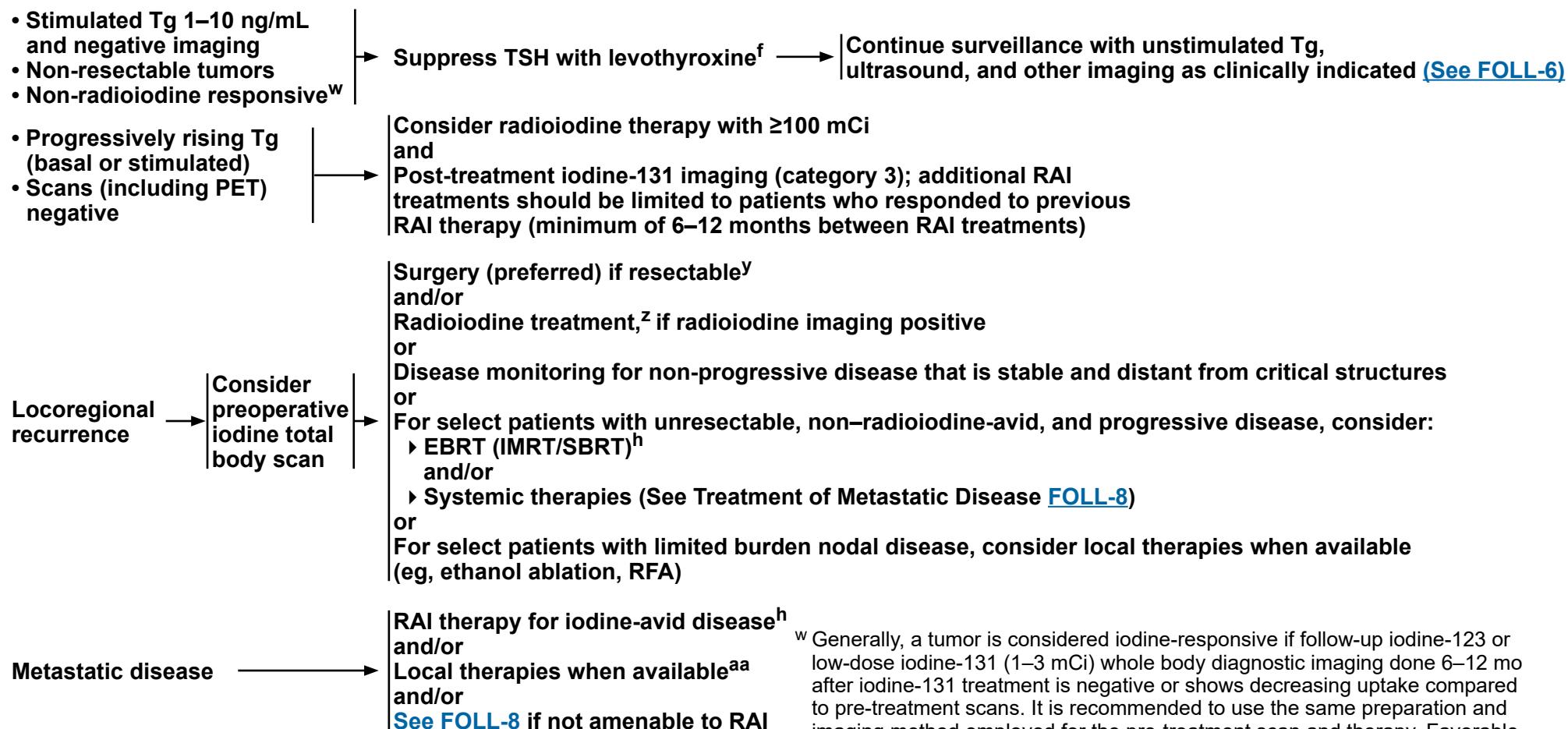
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

### RECURRENT DISEASE



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

<sup>h</sup> See Principles of Radiation and RAI Therapy (THYR-C).

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

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

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

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

<sup>aa</sup> Ethanol ablation, cryoablation, RFA, etc.

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

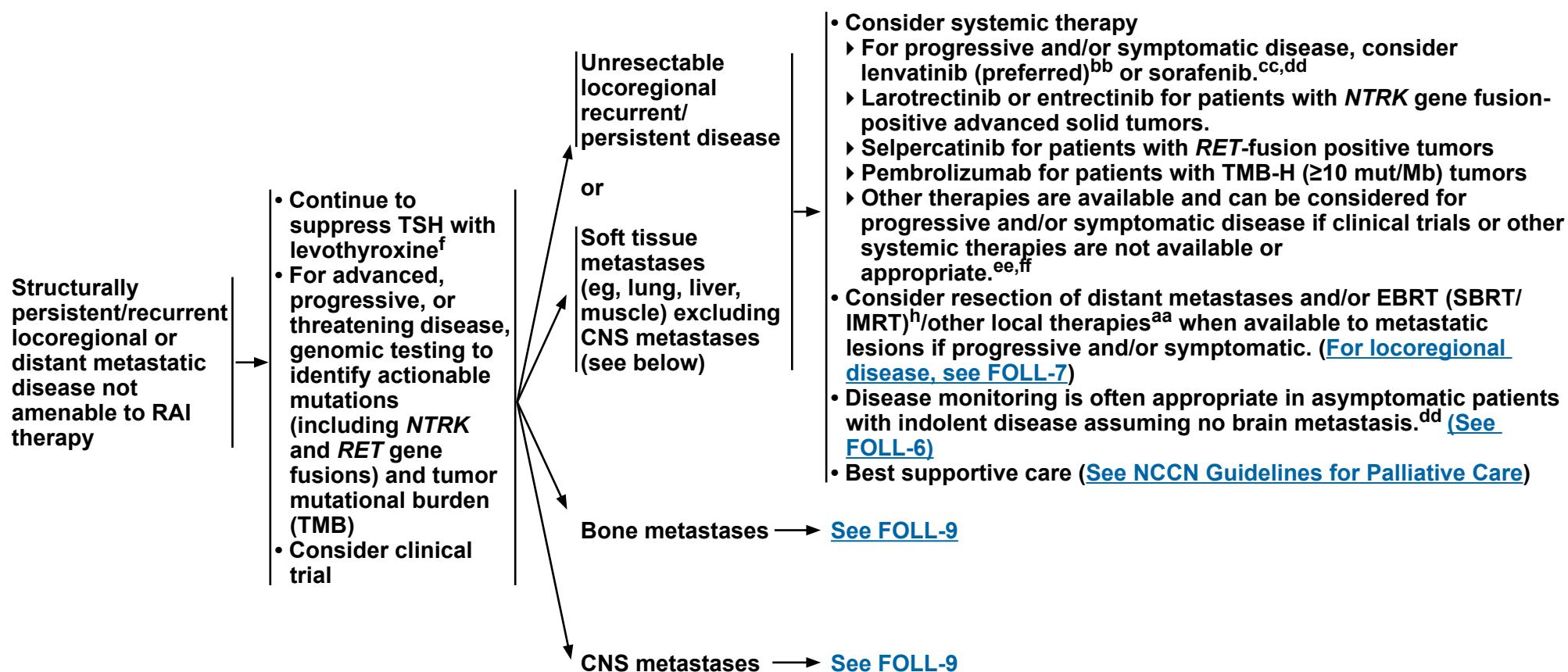
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

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



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

<sup>h</sup> See Principles of Radiation and RAI Therapy (THYR-C).

<sup>aa</sup> Ethanol ablation, cryoablation, RFA, etc.

<sup>bb</sup> In a subset of patients (older than 65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.

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

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

<sup>ee</sup> Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive], dabrafenib [BRAF positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

<sup>ff</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Follicular Carcinoma

### TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY<sup>gg</sup>

- Consider surgical palliation and/or EBRT/SBRT/other local therapies<sup>aa</sup> 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.<sup>hh</sup>
  - Disease monitoring may be appropriate in asymptomatic patients with indolent disease.<sup>dd</sup> ([See FOLL-6](#))
  - Consider systemic therapy
    - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.<sup>cc</sup>
    - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors.
    - Selpercatinib for patients with *RET*-fusion positive tumors
    - Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors
    - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.<sup>dd,ee,ff</sup>
  - Best supportive care ([See NCCN Guidelines for Palliative Care](#))
- 
- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred or
  - For multiple CNS lesions, consider radiotherapy, including image-guided radiotherapy, and/or resection in select cases and/or
  - Consider systemic therapy
    - For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib<sup>cc,ii,jj</sup> and/or
    - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - Selpercatinib for patients with *RET*-fusion positive tumors
    - Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors and/or
    - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.<sup>dd,ee,ff,ii</sup>
  - Best supportive care ([See NCCN Guidelines for Palliative Care](#))

Bone metastases →

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

<sup>aa</sup> Ethanol ablation, cryoablation, RFA, etc.

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

<sup>dd</sup> Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. [See Principles of Kinase Inhibitor Therapy \(THYR-B\)](#).

<sup>ee</sup> Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

<sup>ff</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

<sup>gg</sup> RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

<sup>hh</sup> Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia.

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

<sup>jj</sup> TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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

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



FNA  
RESULTS

DIAGNOSTIC  
PROCEDURES

PRIMARY TREATMENT

Hürthle cell neoplasm<sup>a</sup>  
(Bethesda IV)  
[See THYR-3](#)

- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- CT/MRI with contrast for locally advanced disease or vocal cord paresis<sup>b</sup>
- Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)<sup>c</sup>

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

or

Lobectomy/isthmusectomy

Benign

Hürthle cell carcinoma<sup>e</sup>

Invasive cancer (widely invasive or encapsulated angioinvasive with ≥4 vessels)

Encapsulated angioinvasive with <4 vessels or Minimally invasive HCC<sup>d</sup>

Benign

Levothyroxine therapy to keep TSH normal<sup>f</sup>

Completion of thyroidectomy

Completion of thyroidectomy or Disease monitoring

[See Postsurgical Evaluation \(HÜRT-2\)](#)

- Consider levothyroxine therapy to keep TSH low or normal<sup>f</sup>
- See Disease Monitoring and Maintenance ([HÜRT-6](#))

<sup>a</sup> The diagnosis of Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA.

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

<sup>c</sup> 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.

<sup>d</sup> Minimally invasive HCC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

<sup>e</sup> Also known as oxyphilic, oncocytic, or follicular carcinoma, oncocytic type.

<sup>f</sup> [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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Hürthle Cell Carcinoma

### POSTSURGICAL EVALUATION

No gross residual disease in neck

→ See Consideration for Initial Postoperative RAI Therapy ([HÜRT-3](#))

Gross residual disease in neck → Cross-sectional CT or MRI of neck with contrast → Resectable → Resect, if possible → No gross residual disease → See Consideration for Initial Postoperative RAI Therapy ([HÜRT-3](#))

→ Gross residual disease

→ Unresectable<sup>g</sup>

- TSH + Tg measurement + antithyroglobulin antibodies (6–12 wks postoperatively)
- Iodine-123 or iodine-131<sup>h</sup> total body radioiodine imaging<sup>h</sup> (category 2B)

Suspected or proven inadequate RAI uptake

Adequate RAI uptake or No RAI imaging performed

Suspected or proven inadequate RAI uptake

Adequate RAI uptake or No RAI imaging performed

Monitoring of residual disease or Consider EBRT/IMRT if disease is threatening vital structures<sup>i</sup>

- Radioiodine treatment (preferred)
- Post-treatment iodine-131 whole body imaging
- TSH-stimulated Tg
- Consider EBRT/IMRT<sup>i</sup>

Monitoring of residual disease or Consider systemic therapy ([HÜRT-8](#))

- Radioiodine treatment (preferred)<sup>i</sup>
- Post-treatment iodine-131 whole body imaging
- TSH-stimulated Tg

• Suppress TSH with levothyroxine<sup>f</sup>  
• See [Disease Monitoring and Maintenance \(HÜRT-6\)](#)

For viscerally invasive disease or rapid progression, upfront EBRT/IMRT may be most appropriate<sup>i</sup>

- TSH + Tg measurement + antithyroglobulin antibodies (6–12 wks postoperatively)
- Iodine-123 or iodine-131<sup>h</sup> total body radioiodine imaging<sup>h</sup> (category 2B)

<sup>f</sup> [See Principles of TSH Suppression \(THYR-A\)](#).

<sup>g</sup> For bulky, locoregional, viscerally invasive disease or rapid progression, refer to high-volume multidisciplinary institution, including radiation oncology referral.

<sup>h</sup> If considering dosimetry iodine-131 is the preferred agent.

<sup>i</sup> [See Principles of Radiation and RAI Therapy \(THYR-C\)](#).

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Hürthle Cell Carcinoma

### CLINICOPATHOLOGIC FACTORS<sup>j</sup>

RAI not typically recommended (if all present):

- Largest primary tumor <2 cm
- Intrathyroidal
- No vascular invasion
- Clinical N0
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL<sup>k</sup>
- Negative postoperative ultrasound, if done<sup>l</sup>

RAI selectively recommended (if any present):

- Largest primary tumor 2–4 cm
- Minor vascular invasion<sup>d</sup>
- Cervical lymph node metastases
- Postoperative unstimulated Tg <5–10 ng/mL<sup>k</sup>
- Microscopic positive margins

RAI recommended (if any present):

- Gross extrathyroidal extension
- Primary tumor >4 cm
- Extensive vascular invasion<sup>d</sup>
- Postoperative unstimulated Tg >5–10 ng/L<sup>k,m</sup>
- Bulky or >5 positive lymph nodes

Known or suspected distant metastases at presentation

### CONSIDERATION FOR INITIAL POSTOPERATIVE USE OF RAI AFTER TOTAL THYROIDECTOMY

RAI not typically indicated  
(See HÜRT-6)

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

RAI being considered  
(See HÜRT-4)

Amenable to RAI (See HÜRT-5)

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

<sup>d</sup> Minimally invasive HCC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

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

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

<sup>l</sup> If preoperative imaging incomplete, consider postoperative ultrasound including central and lateral neck components.

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

<sup>m</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.

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

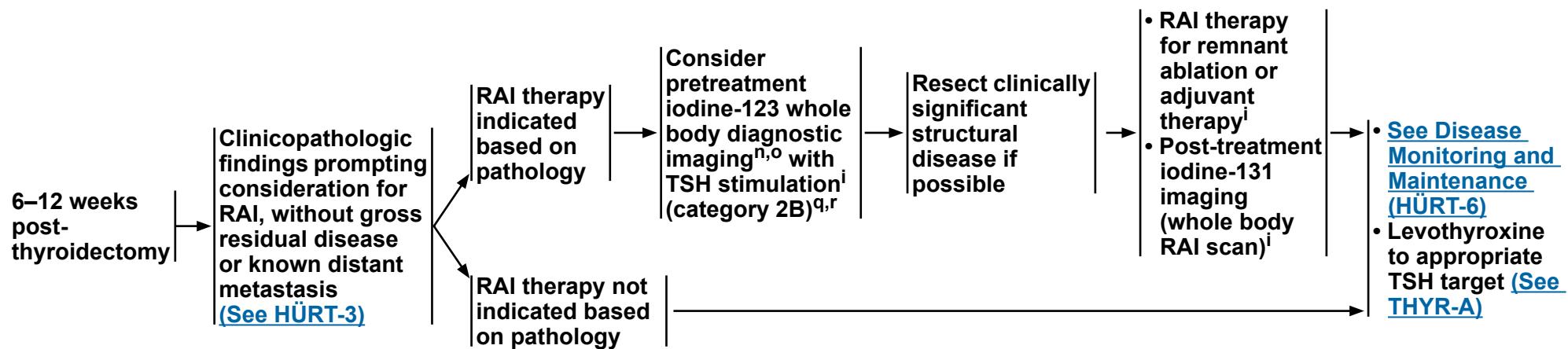
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Hürthle Cell Carcinoma

### RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES



<sup>i</sup> See Principles of Radiation and RAI Therapy (THYR-C).

<sup>n</sup> Even in the absence of thyroid bed uptake RAI treatment may be considered. If higher than expected uptake (residual thyroid uptake or distant metastasis) change dose accordingly.

<sup>o</sup> A false-negative pretreatment scan is possible and should not prevent the use of RAI if otherwise indicated.

<sup>q</sup> Alternatively, low-dose iodine-131 (1–3 mCi) may be used.

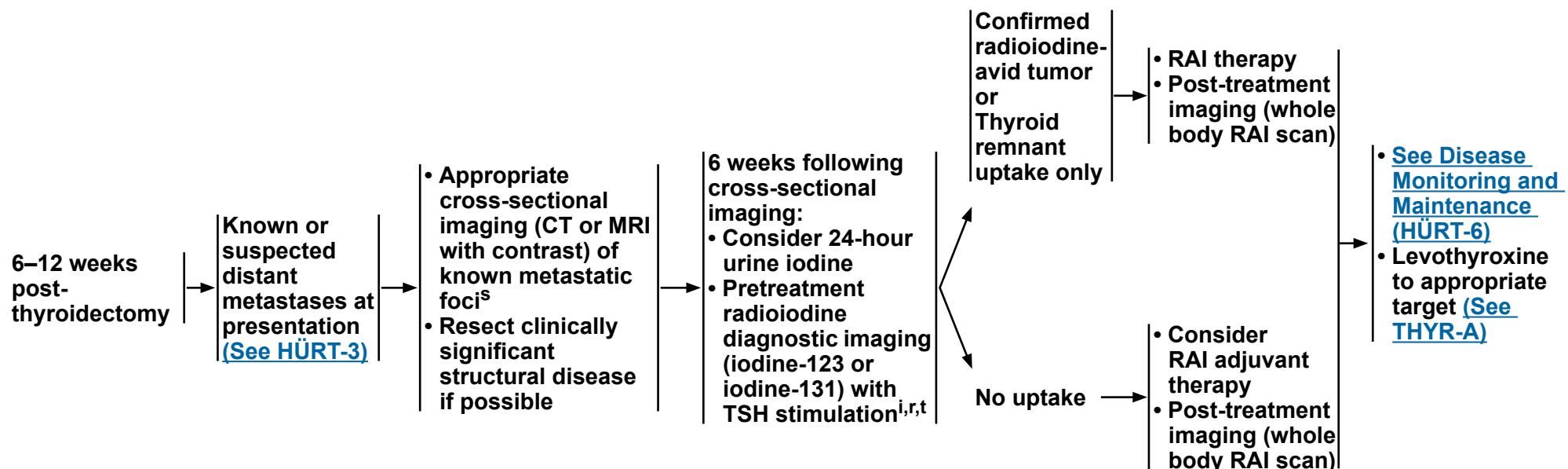
<sup>r</sup> While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, 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.

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

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



**KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE**



<sup>i</sup> See Principles of Radiation and RAI Therapy (THYR-C).

<sup>r</sup> 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.

<sup>t</sup> To evaluate macroscopic metastatic foci for potential alternative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression.

<sup>s</sup> Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

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

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



**DISEASE MONITORING AND MAINTENANCE**

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound<sup>u</sup>
- 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<sup>v</sup>
- Consider TSH-stimulated radioiodine whole body imaging in high-risk patients, patients with previous RAI-avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance

**FINDINGS**

→ NED →

→ Abnormal findings →

**MANAGEMENT**

**Long-term disease monitoring<sup>w</sup>**

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

→ Recurrent disease  
(See HÜRT-7)

**Additional workup**

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

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

<sup>u</sup>A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

<sup>v</sup>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.

<sup>w</sup>[See NCCN Guidelines for Survivorship.](#)

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

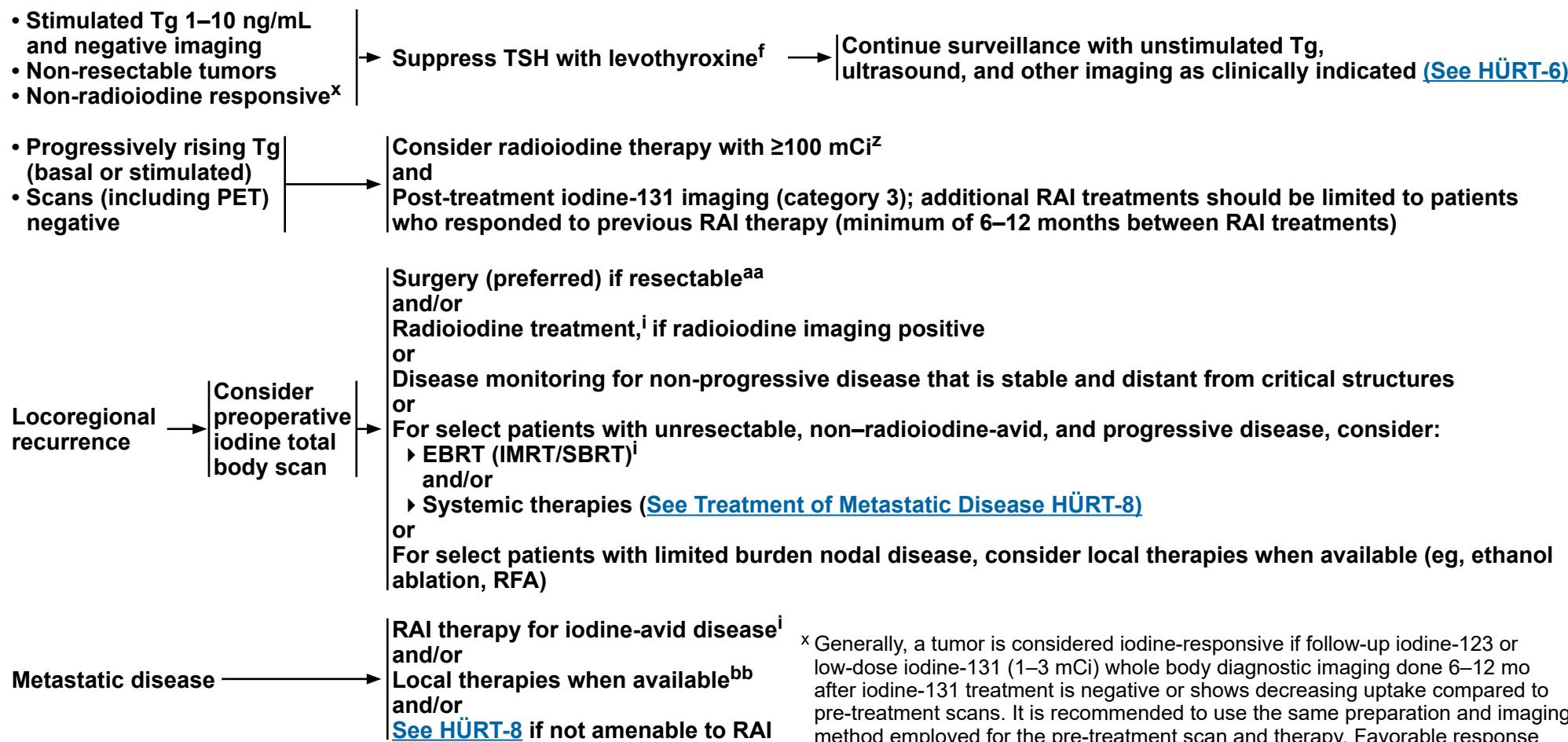
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Hürthle Cell Carcinoma

### RECURRENT DISEASE



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

<sup>i</sup> See Principles of Radiation and RAI Therapy (THYR-C).

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

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

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

<sup>bb</sup> Ethanol ablation, cryoablation, RFA, etc.

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

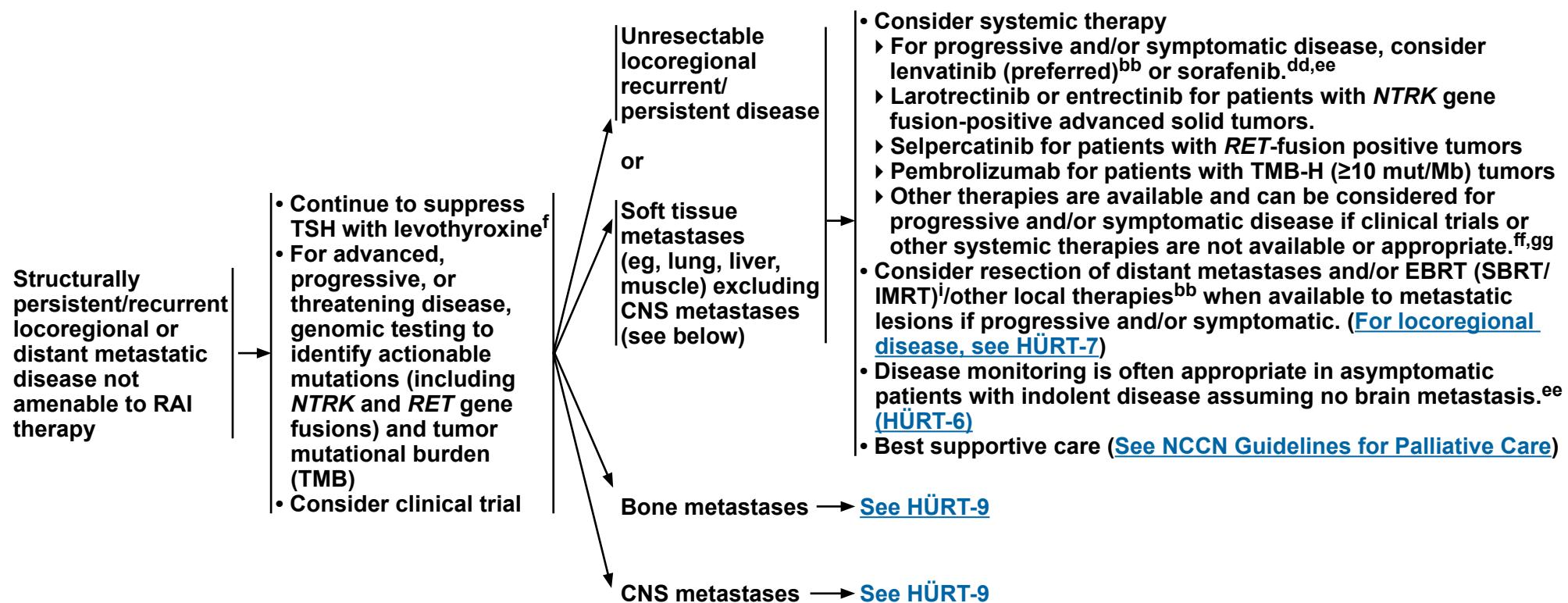
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Hürthle Cell Carcinoma

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



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

<sup>i</sup> See Principles of Radiation and RAI Therapy (THYR-C).

<sup>bb</sup> Ethanol ablation, cryoablation, RFA, etc.

<sup>cc</sup> In a subset of patients (older than 65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.

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

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

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

<sup>gg</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Hürthle Cell Carcinoma

### TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY<sup>hh</sup>

- Consider surgical palliation and/or EBRT/SBRT/other local therapies<sup>bb</sup> 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.<sup>ii</sup>
  - Disease monitoring may be appropriate in asymptomatic patients with indolent disease.<sup>ee</sup> (**HÜRT-6**)
  - Consider systemic therapy
    - ▶ For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.<sup>dd</sup>
    - ▶ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors.
    - ▶ Selpercatinib for patients with *RET*-fusion positive tumors
    - ▶ Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors
    - ▶ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.<sup>ee,ff,gg</sup>
  - Best supportive care ([See NCCN Guidelines for Palliative Care](#))
- 
- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred or
  - For multiple CNS lesions, consider radiotherapy, including image-guided radiotherapy, and/or resection in select cases and/or
  - Consider systemic therapy
    - ▶ For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib<sup>dd,jj,kk</sup> and/or
    - ▶ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ▶ Selpercatinib for patients with *RET*-fusion positive tumors
    - ▶ Pembrolizumab for patients with TMB-H ( $\geq 10$  mut/Mb) tumors and/or
    - ▶ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.<sup>ee,ff,gg,jj</sup>
  - Best supportive care ([See NCCN Guidelines for Palliative Care](#))

Bone metastases →

CNS metastases →

<sup>bb</sup> Ethanol ablation, cryoablation, RFA, etc.

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

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

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

<sup>gg</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

<sup>hh</sup> RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.

<sup>ii</sup> Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia.

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

<sup>kk</sup> TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

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

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



**CLINICAL PRESENTATION**      **DIAGNOSTIC PROCEDURES**

Medullary thyroid carcinoma on FNA

- Basal serum calcitonin level
- CEA
- Pheochromocytoma screening<sup>b</sup>
- Serum calcium
- Consider genetic counseling
- Screen for germline *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>
- Additional cross-sectional imaging as indicated:<sup>f</sup>
  - ▶ Consider contrast-enhanced CT of neck/ chest and liver MRI or 3-phase CT of liver<sup>e,f</sup>
  - ▶ Consider Ga-68 DOTATATE PET/CT; if not available consider bone scan and/or skeletal MRI

≥1.0 cm in diameter or bilateral thyroid disease

<1.0 cm in diameter and unilateral thyroid disease

**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

Total thyroidectomy and consider neck dissection (level VI)

See Management 2–3 Months Postoperative ([MEDU-5](#))

Medullary thyroid carcinoma diagnosed after initial thyroid surgery

Germline mutation of *RET* proto-oncogene<sup>a,b</sup>

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

<sup>b</sup>Evidence of pheochromocytoma should be evaluated and addressed appropriately before proceeding to the next step on the pathway.

<sup>c</sup>Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.

[See Additional Workup and Management \(MEDU-2\)](#)

[See Additional Workup and Primary Treatment \(MEDU-3\)](#)

<sup>d</sup>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.

<sup>e</sup>Having distant metastases does not mean that surgery is contraindicated.

<sup>f</sup>Imaging may be indicated based on high burden of disease, calcitonin >400 pg/mL, or elevated CEA levels.

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

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



**CLINICAL  
PRESENTATION**

**ADDITIONAL WORKUP**

**MANAGEMENT**

Medullary thyroid carcinoma diagnosed after initial thyroid surgery<sup>g</sup>

- Basal serum calcitonin level
- CEA
- Screen for germline *RET* proto-oncogene mutations<sup>c,h</sup> (exons 10, 11, 13–16) with genetic counseling
- Central and lateral neck compartments ultrasound, if not previously done

Germline *RET* mutation identified

See Additional Workup and Primary Treatment ([\(MEDU-3\)](#))

Germline *RET* mutation not identified

See Management 2–3 Months Postoperative ([\(MEDU-5\)](#))

<sup>c</sup> Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.

<sup>g</sup> If initial thyroid surgery was less than a total thyroidectomy, additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) may not be necessary unless there is a positive germline *RET* mutation or radiographic evidence of disease (ie, biopsy-proven residual neck disease).

<sup>h</sup> Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Medullary Carcinoma

### CLINICAL PRESENTATION

### ADDITIONAL WORKUP

### PRIMARY TREATMENT

Germline mutation of *RET* proto-oncogene<sup>a,c</sup>

Multiple endocrine neoplasia (MEN2B) (RET mutations)<sup>i</sup>

- Basal serum calcitonin level<sup>j</sup>
- CEA
- Pheochromocytoma screening<sup>b,k</sup>
- Central and lateral neck compartments ultrasound,<sup>l</sup> if not previously done
- Neck CT with contrast

- Total thyroidectomy during the first year of life or at diagnosis<sup>a</sup>
- 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
- Postoperative administration of levothyroxine to normalize TSH

→ See Management 2–3 Months Postoperative ([MEDU-5](#))

MEN2A/Familial medullary thyroid carcinoma (FMTC) (RET mutations)<sup>i</sup>

- Basal serum calcitonin level<sup>j</sup>
- CEA
- Pheochromocytoma screening<sup>b,k</sup>
- Serum calcium + parathyroid hormone (PTH)
- Central and lateral neck compartments ultrasound,<sup>l</sup> if not previously done
- Neck CT with contrast

→ See Primary Treatment ([MEDU-4](#))

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

<sup>b</sup> Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.

<sup>c</sup> Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.

<sup>i</sup> The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other *RET* mutations associated with MEN2A or FMTC are generally moderate risk. Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, et al. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Wells SA, et al. Thyroid 2015;25(6):567-610.)

<sup>j</sup> Normal calcitonin ranges have not been established for very young children.

<sup>k</sup> Screening for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A) should be performed annually. For some *RET* mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.

<sup>l</sup> In addition to ultrasound, parathyroid imaging may include sestamibi scan with SPECT or 4D-CT depending on institutional practice/protocol.

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

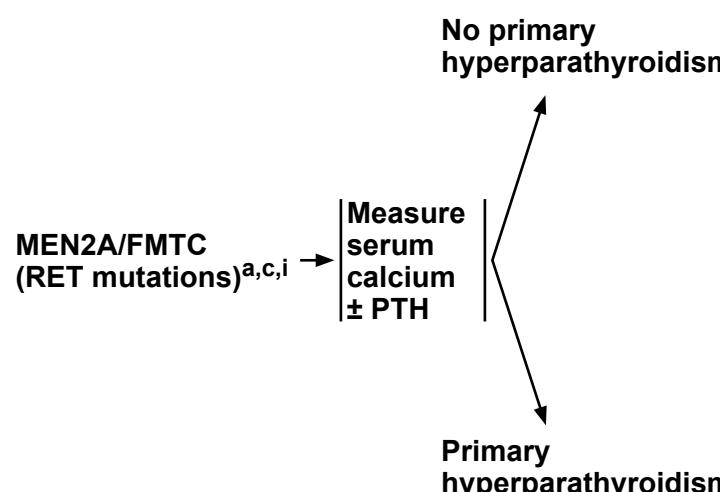
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Medullary Carcinoma

### CLINICAL PRESENTATION



### PRIMARY TREATMENT

- 
- ```
graph LR; C[No primary hyperparathyroidism] --> E[Total thyroidectomy by age 5a,i or when mutation identifieda (if mutation identified at older age)]; E --> F[Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitoninm or CEA test or ultrasound identified thyroid or nodal abnormality]; F --> G[Consider prophylactic ipsilateral modified neck dissection if there is high-volume or gross disease in the adjacent central neck]; G --> H[Consider more extensive lymph node dissection (levels II–V) if tumor(s) >1.0 cm or central node(s) positive]; H --> I[Postoperative administration of levothyroxine to normalize TSH]; I --> J[See Management 2–3 Months Postoperative (MEDU-5)]
```
- No primary hyperparathyroidism:**
- Total thyroidectomy by age 5<sup>a,i</sup> or when mutation identified<sup>a</sup> (if mutation identified at older age)
  - Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin<sup>m</sup> or CEA test or ultrasound identified thyroid or nodal abnormality
  - Consider prophylactic ipsilateral modified neck dissection if there is high-volume or gross disease in the adjacent central neck
  - Consider more extensive lymph node dissection (levels II–V) if tumor(s) >1.0 cm or central node(s) positive
  - Postoperative administration of levothyroxine to normalize TSH
- Primary hyperparathyroidism:**
- See Primary Treatment as outlined above
  - During primary operative procedure and parathyroid exploration:
    - If single adenoma, excise
    - If multiglandular disease, autotransplant or leave the equivalent mass of one normal parathyroid gland
    - Consider cryopreservation of parathyroid tissue
- Both pathways lead to 'See Management 2–3 Months Postoperative (MEDU-5)'.

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

<sup>c</sup>Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.

<sup>i</sup> The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other *RET* mutations associated with MEN2A or FMTC are generally moderate risk. Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, et al. J Clin Endocrinol Metab 2001;86:5658–5671 and American Thyroid Association Guidelines Task Force. Wells SA, et al. Thyroid 2015;25:567–610.)

<sup>m</sup>Prophylactic neck dissection may not be required if serum calcitonin is less than 40 ng/mL, because lymph node metastases are unlikely with minor calcitonin elevations in this setting.

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

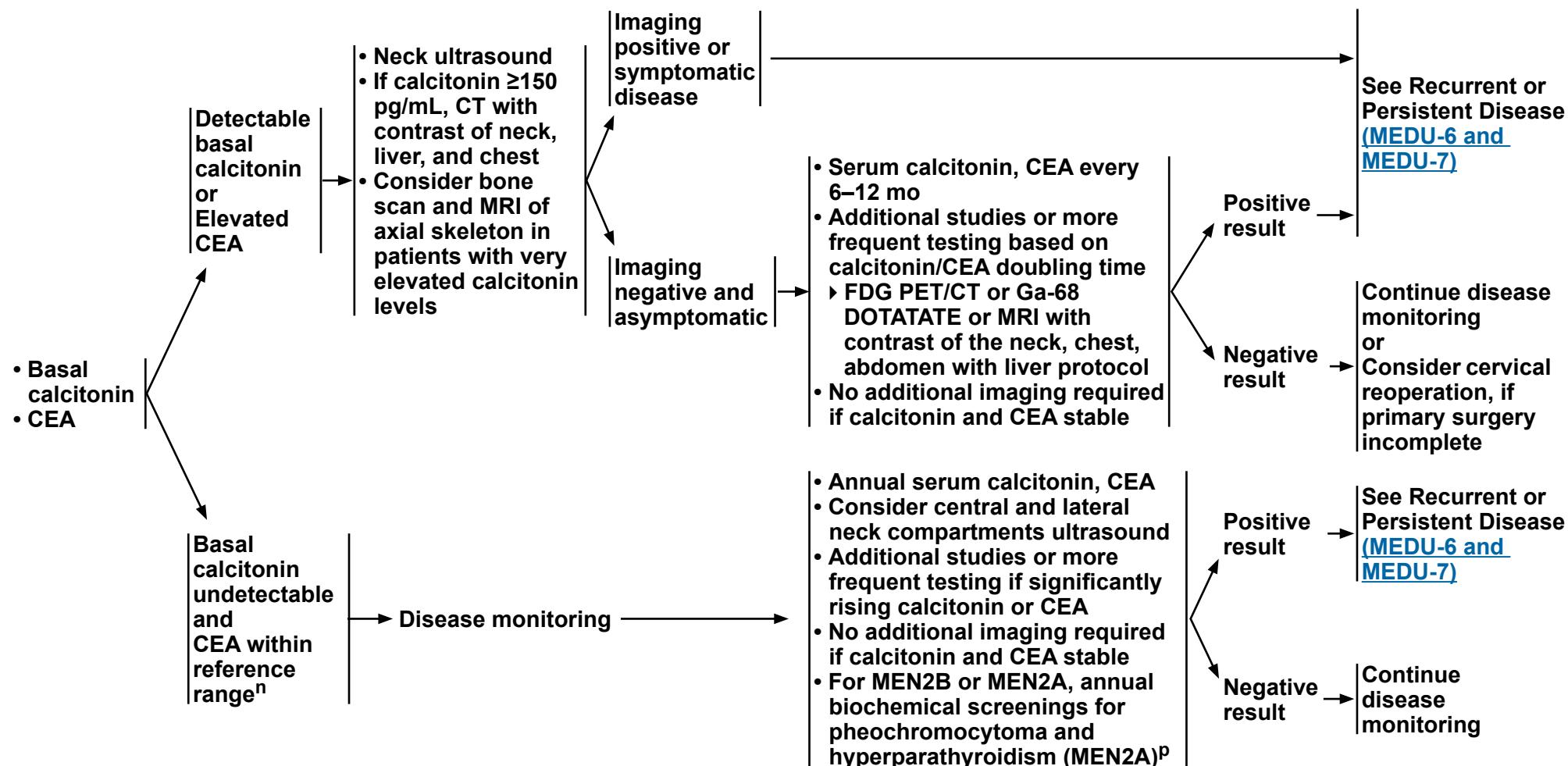
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Medullary Carcinoma

### MANAGEMENT 2–3 MONTHS POSTOPERATIVE



<sup>n</sup>The likelihood of significant residual disease with an undetectable basal calcitonin is very low.

<sup>o</sup>See [NCCN Guidelines for Survivorship](#).

<sup>p</sup>See page PHEO-1 from the [NCCN Guidelines for Neuroendocrine and Adrenal Tumors](#).

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

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



**RECURRENT OR PERSISTENT DISEASE**      **TREATMENT**  
**LOCOREGIONAL DISEASE**

Locoregional

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

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

<sup>q</sup>Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.

<sup>r</sup>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.

<sup>s</sup>Genomic testing including tumor mutational burden (TMB) or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.

<sup>t</sup>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 \(THYR-B\).](#)

<sup>u</sup>Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Medullary Carcinoma

### RECURRENT OR PERSISTENT DISEASE DISTANT METASTASES

Asymptomatic disease

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

Progressive disease,  
see pathway below

Symptomatic disease  
or  
progression<sup>t</sup>

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

<sup>q</sup> Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.

<sup>r</sup> Only health care professionals and pharmacies certified through the vandetanib REMS program, a restricted distribution program, will be able to prescribe and dispense the drug.

<sup>s</sup> Genomic testing including tumor mutational burden (TMB) or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.

<sup>t</sup> 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 \(THYR-B\).](#)

<sup>u</sup> Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

<sup>v</sup> Clinical benefit can be seen in both sporadic and familial MTC.

<sup>w</sup> While not FDA approved for treatment of medullary thyroid cancer, other commercially available small-molecule kinase inhibitors (such as sorafenib, sunitinib, lenvatinib, or pazopanib) can be considered if clinical trials or preferred systemic therapy options are not available or appropriate, or if the patient progresses on preferred systemic therapy options.

<sup>x</sup> Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine or fluorouracil/dacarbazine alternating with fluorouracil/streptozocin.

<sup>y</sup> Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

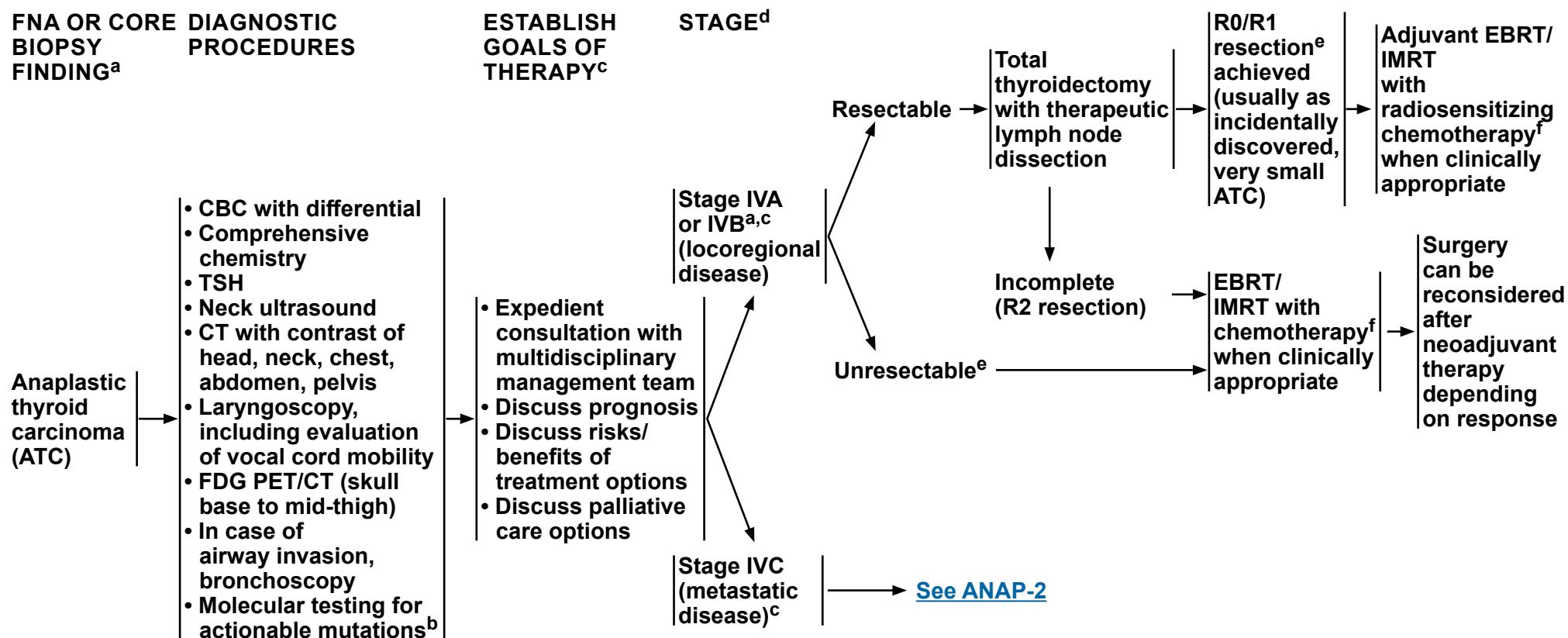
Note: All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Anaplastic Carcinoma



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

<sup>b</sup> Molecular testing should include *BRAF*, *NTRK*, *ALK*, *RET*, and tumor mutational burden.

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

<sup>d</sup> [See Staging \(ST-1\)](#).

<sup>e</sup> Resectability for locoregional disease depends on extent of involved structures, potential morbidity, and mortality associated with resection. In most cases, there is no indication for a debulking surgery. [See Staging \(ST-1\)](#) for definitions of R0/R1/R2.

<sup>f</sup> [See Adjuvant/Radiosensitizing Chemotherapy Regimens for Anaplastic Thyroid Carcinoma \(ANAP-A \[1 of 2\]\)](#).

[See Disease Monitoring and Management on ANAP-2](#)

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

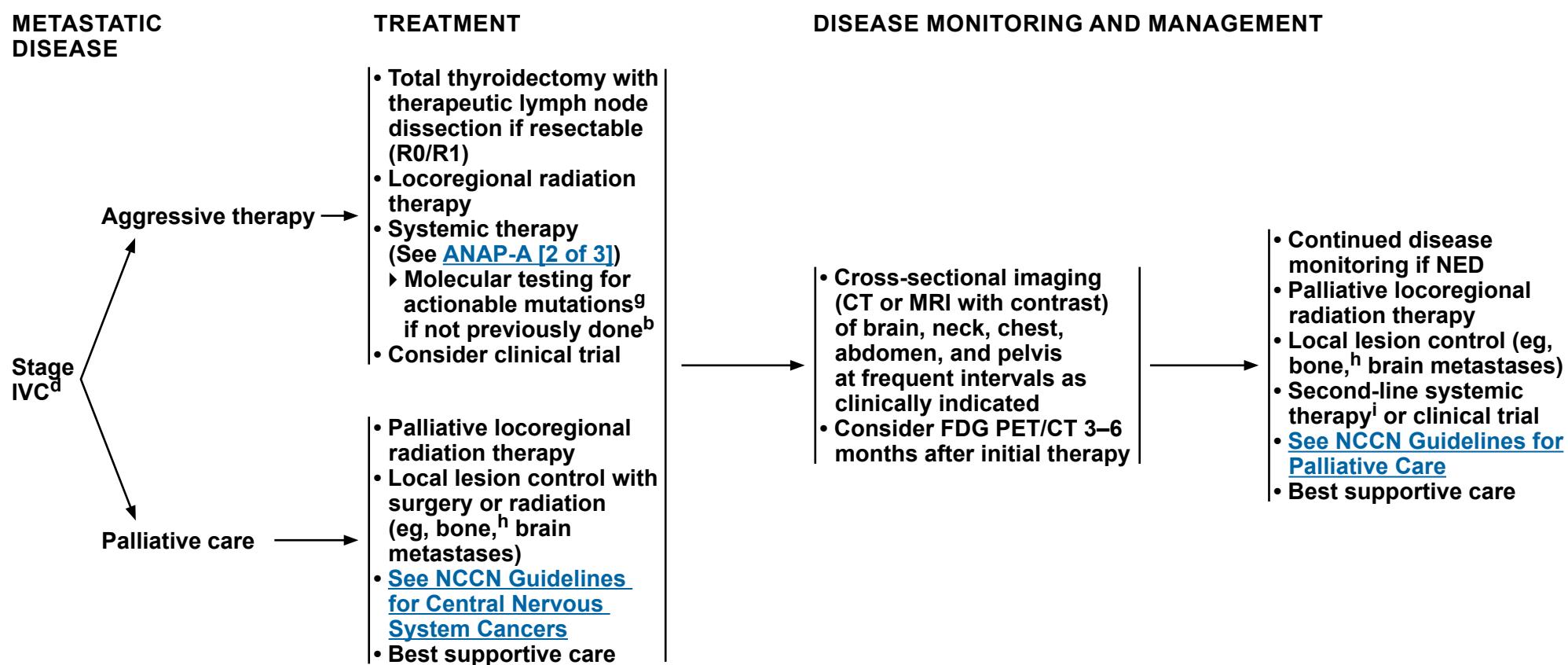
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Anaplastic Carcinoma

### METASTATIC DISEASE



<sup>b</sup> Molecular testing should include *BRAF*, *NTRK*, *ALK*, *RET*, and tumor mutational burden.

<sup>d</sup> [See Staging \(ST-1\)](#).

<sup>g</sup> Consider dabrafenib/trametinib if *BRAF* V600E mutation positive [Subbiah V, et al. J Clin Oncol 2018;36(1):7-13]; larotrectinib or entrectinib if *NTRK* gene fusion positive [Drilon A, et al. N Engl J Med 2018;378(8):731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282]; selpercatinib if *RET* fusion positive (Wirth L, et al. Presented at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27–October 1, 2019. Oral presentation.) or pembrolizumab for TMB-H (Marabelle A, et al. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019).

<sup>h</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.

<sup>i</sup> [See Systemic Therapy Regimens for Metastatic Disease \(ANAP-A \[2 of 2\]\)](#).

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

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



### SYSTEMIC THERAPY

| Adjuvant/Radiosensitizing Chemotherapy Regimens <sup>1</sup> |                                                                                                                                                                             |                           |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Other Recommended Regimens                                   |                                                                                                                                                                             |                           |
| Paclitaxel/carboplatin                                       | Paclitaxel 50 mg/m <sup>2</sup> , carboplatin AUC 2 IV                                                                                                                      | Weekly                    |
| Docetaxel/doxorubicin                                        | Docetaxel 60 mg/m <sup>2</sup> IV, doxorubicin 60 mg/m <sup>2</sup> IV (with pegfilgrastim)<br>or<br>Docetaxel 20 mg/m <sup>2</sup> IV, doxorubicin 20 mg/m <sup>2</sup> IV | Every 3–4 weeks<br>Weekly |
| Paclitaxel                                                   | 30–60 mg/m <sup>2</sup> IV                                                                                                                                                  | Weekly                    |
| Cisplatin                                                    | 30–40 mg/m <sup>2</sup> IV                                                                                                                                                  | Weekly                    |
| Doxorubicin                                                  | 60 mg/m <sup>2</sup> IV<br>or<br>20 mg/m <sup>2</sup> IV                                                                                                                    | Every 3 weeks<br>Weekly   |

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

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

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma – Anaplastic Carcinoma

### SYSTEMIC THERAPY

| Systemic Therapy Regimens for Metastatic Disease                                                                        |                                                                                                                                                                             |                                    |
|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| <b>Preferred Regimens</b>                                                                                               |                                                                                                                                                                             |                                    |
| Dabrafenib/trametinib <sup>2</sup><br>(BRAF V600E mutation positive)                                                    | Dabrafenib 150 mg PO<br>and<br>Trametinib 2 mg PO                                                                                                                           | Twice daily<br><br>Once daily      |
| Larotrectinib <sup>3</sup><br>(NTRK gene fusion positive)                                                               | 100 mg PO                                                                                                                                                                   | Twice daily                        |
| Entrectinib <sup>4</sup><br>(NTRK gene fusion positive)                                                                 | 600 mg PO                                                                                                                                                                   | Once daily                         |
| Selpercatinib <sup>5</sup><br>(RET-fusion positive)                                                                     | 120 mg PO (< 50 kg)<br>or<br>160 mg PO (≥ 50 kg)                                                                                                                            | Twice daily                        |
| <b>Other Recommended Regimens</b>                                                                                       |                                                                                                                                                                             |                                    |
| Paclitaxel/carboplatin <sup>1</sup>                                                                                     | Paclitaxel 60–100 mg/m <sup>2</sup> , carboplatin AUC 2 IV<br>or<br>Paclitaxel 135–175 mg/m <sup>2</sup> , carboplatin AUC 5–6 IV                                           | Weekly<br><br>Every 3–4 weeks      |
| Docetaxel/doxorubicin <sup>1</sup>                                                                                      | Docetaxel 60 mg/m <sup>2</sup> IV, doxorubicin 60 mg/m <sup>2</sup> IV (with pegfilgrastim)<br>or<br>Docetaxel 20 mg/m <sup>2</sup> IV, doxorubicin 20 mg/m <sup>2</sup> IV | Every 3–4 weeks<br><br>Weekly      |
| Paclitaxel <sup>1</sup>                                                                                                 | 60–90 mg/m <sup>2</sup> IV<br>or<br>135–200 mg/m <sup>2</sup> IV                                                                                                            | Weekly<br><br>Every 3–4 weeks      |
| Doxorubicin <sup>1</sup>                                                                                                | 60–75 mg/m <sup>2</sup> IV<br>or<br>20 mg/m <sup>2</sup> IV                                                                                                                 | Every 3 weeks<br><br>Weekly        |
| <b>Useful in Certain Circumstances</b>                                                                                  |                                                                                                                                                                             |                                    |
| Lenvatinib <sup>6</sup><br>(if not tolerating or no response to recommended agents in patients without curative option) | 24 mg PO                                                                                                                                                                    | Daily                              |
| Pembrolizumab <sup>7</sup><br>(TMB-H [≥10 mut/Mb])                                                                      | 200mg IV<br>or<br>400mg IV                                                                                                                                                  | Every 3 weeks<br><br>Every 6 weeks |

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

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

[References](#)

ANAP-A  
2 OF 3



## SYSTEMIC THERAPY REFERENCES

- <sup>1</sup> Adapted with permission from Mary Ann Liebert, Inc., Smallridge RC, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid* 2012;22:1121.
- <sup>2</sup> Subbiah V, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *J Clin Oncol* 2018;36(1):7-13.
- <sup>3</sup> Drilon A, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;378(8):731-739.
- <sup>4</sup> Doebele RC, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271-282.
- <sup>5</sup> Wirth L, et al. Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET-altered thyroid cancers. Presented at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27–October 1, 2019. Oral presentation.
- <sup>6</sup> Tahara M, et al. Lenvatinib for anaplastic thyroid cancer. *Front Oncol* 2017;7:25.
- <sup>7</sup> Marabelle A, et al. Association of tumor mutational burden with outcomes in patients with select advanced solid tumors treated with pembrolizumab in KEYNOTE-158. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019.

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

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



### PRINCIPLES OF THYROID-STIMULATING HORMONE (TSH) SUPPRESSION

- Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH.
  - ▶ In general, patients with known structural residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range.
  - ▶ For low-risk patients with biochemical evidence but no structural evidence of disease (eg, Tg positive, but imaging negative), maintain TSH levels at 0.1–0.5 mU/L.
- Patients who remain disease free for several years can probably have their TSH levels maintained within the reference range (0.5–2 mU/L).
  - ▶ Given the potential toxicities associated with TSH-suppressive doses of levothyroxine—including cardiac tachyarrhythmias (especially in the elderly) and bone demineralization (particularly in post-menopausal women) as well as frank symptoms of thyrotoxicosis—the risks and benefits of TSH-suppressive therapy must be balanced for each individual patient.
  - ▶ Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/day) and vitamin D (1000 units/day).

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

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



## PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA<sup>1-7</sup>

- Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic medullary thyroid cancer (MTC) and in radioiodine-refractory differentiated thyroid cancer (DTC).
- When considering kinase inhibitor therapy for individual patients, several factors should be considered.
  - ▶ Kinase inhibitor therapy can be associated with improved progression-free survival, but is not curative.
  - ▶ Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.
  - ▶ The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.
- The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have drug-induced side effects.
- Optimal management of kinase inhibitor side effects is essential. Where available, guidelines outlining the management of the dermatologic, hypertensive, and gastrointestinal side effects of kinase inhibitors can be used; side effects have been fatal. In addition, dose modification may be required, including dose holds and dose reductions.
- Molecular testing has been shown to be beneficial when making targeted therapy decisions, particularly related to drug therapies or clinical trial participation. In addition, the presence of some mutations may have prognostic importance.

<sup>1</sup>Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30:134-141.

<sup>2</sup>Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. *Lancet* 2014;384(9940):319-328.

<sup>3</sup>Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;31:3639-3646.

<sup>4</sup>Burtness B, Anadkat M, Basti S, et al. NCCN Task Force Report: Management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer. *J Natl Compr Canc Netw* 2009;7 Suppl 1:S5-S21.

<sup>5</sup>Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician's perspective. *Semin Oncol* 2014;41 Suppl 2:S1-S16.

<sup>6</sup>Carhill AA, Cabanillas ME, Jimenez C, et al. The noninvestigational use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. *J Clin Endocrinol Metab* 2013;98:31-42.

<sup>7</sup>Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372(7):621-30.

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

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



**General Principles**

**PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY**  
**IODINE-131 ADMINISTRATION**

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

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

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

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

[Continued](#)  
[References](#)

THYR-C  
1 OF 5



## PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY IODINE-131 ADMINISTRATION

### Administered Activity

See special circumstances below for pediatric dose adjustment.

- Remnant ablation:
  - ▶ 30–50 mCi
    - ◊ If RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, in the absence of other adverse pathologic, laboratory, or imaging features, 30 mCi of iodine-131 is recommended (category 1) following either thyrotropin alfa stimulation or thyroid hormone withdrawal. This dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1–4 cm) with small volume N1a disease (fewer than 5 lymph node metastases <2 mm in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.<sup>4,5</sup>
- Adjuvant therapy:
  - ▶ 50–100 mCi
    - ◊ For higher likelihood of residual disease based on operative pathology or pretherapy radioiodine scan
  - ▶ 100–200 mCi
    - ◊ For proven unresectable metastatic disease based on pathology or pretherapy radioiodine scan
  - ▶ Dosimetry can be used to determine maximal dose at high-volume centers for documented nonresectable, large-volume, iodine-concentrating, residual, or recurrent disease. Generally, the maximum 48-hour whole-body dose should not exceed ~80 mCi to avoid pulmonary fibrosis in the case of diffuse lung metastases, and the bone marrow retention maximum should not exceed ~120 mCi at 48 hours.<sup>1</sup>

### Special Circumstances

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

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

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

### Special Circumstances

- RAI after imaging study or procedure using iodine contrast agent:
  - ▶ Wait 1–2 months to allow for free iodine levels to decrease (<100 mcg/24 hours) and allow for optimal RAI uptake<sup>7,8</sup>
  - ▶ Consider measurement of 24-hour urine iodine to confirm a normal free iodine prior to preparing for dosing.
- Breastfeeding patients:
  - ▶ Wait 3–6 months after cessation of lactation or with normalization of serum prolactin levels.
  - ▶ Complete cessation of breastfeeding after iodine-123 or iodine-131 administration for the current infant. There should be no increased risk to mother or infant for breastfeeding with subsequent births assuming no radioiodine is administered around the subsequent birth/breastfeeding period.<sup>9</sup>
- Decreased GFR/end-stage renal disease (ESRD)/hemodialysis:
  - ▶ Special consideration to administered dose, and timing with respect to dialysis to maximize therapeutic effect and minimize non-thyroid uptake/exposure<sup>10</sup>
  - ▶ Multidisciplinary involvement including close monitoring by radiation safety to coordinate administration, monitoring, and minimization of exposure to others
- Patients desiring pregnancy
  - ▶ Women should be counseled to wait at least 6 months after iodine-131 therapy to attempt pregnancy to avoid adverse pregnancy outcomes (such as fetal hypothyroidism, malformation, increased malignancy risk in the child, or fetal demise [with high doses]) related to RAI. For many patients a longer interval before attempting pregnancy may be recommended in order to confirm disease-free status at 6–12 months post-RAI. In these cases, earlier pregnancy is inadvisable as it would interfere with disease detection and further management.
  - ▶ In selective cases when doses are high or other considerations are present, integrating care with reproductive endocrinology/oncofertility for men and women may be appropriate.

[Continued](#)  
[References](#)



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

**General Principles**

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

**Treatment Volumes**

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

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

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

[Continued](#)  
[References](#)

THYR-C  
3 OF 5



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

**Dose and Fractionation**

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

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

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

**Anaplastic Thyroid Cancer**

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

**References**

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

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



## PRINCIPLES OF RADIATION AND RADIOACTIVE IODINE THERAPY REFERENCES

- <sup>1</sup>Edmonds CJ, Hayes S, Kermode JC, Thompson BD. Measurement of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine. *Br J Radiol.* 1977;50:799-807.
- <sup>2</sup>Klubo-Gwiezdinska J, Burman KD, Van Nostrand D, et al. Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. *Thyroid.* 2012;22:310-317.
- <sup>3</sup>Tala H, Robbins R, Fagin JA, et al. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. *J Clin Endocrinol Metab.* 2011;96:2105-2111.
- <sup>4</sup>Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med.* 2012;366:1674-1685.
- <sup>5</sup>Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med.* 2012;366:1663-1673.
- <sup>6</sup>Reynolds JC. Comparison of I-131 Absorbed Radiation doses in children and adults: A tool for estimating therapeutic I-131 doses in children. Robbins J, Ed., *Treatment of Thyroid Cancer in Childhood. Proceedings of a Workshop held Sept 10-11, 1992 at the National Institutes of Health,* pp 127-136, 1994.
- <sup>7</sup>Padovani RP, Kasamatsu TS, Nakabashi CC, et al. One month is sufficient for urinary iodine to return to its baseline value after the use of water-soluble iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy. *Thyroid.* 2012;22:926-930.
- <sup>8</sup>Nimmons GL, Funk GF, Graham MM, et al. Urinary iodine excretion after contrast computed tomography scan: implications for radioactive iodine use. *JAMA Otolaryngol Head Neck Surg.* 2013;139:479-482.
- <sup>9</sup>Stabin MG, Breitz HB. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. *J Nucl Med.* 2000;41:863-873.
- <sup>10</sup>Holst JP, Burman KD, Atkins F, et al. Radioiodine therapy for thyroid cancer and hyperthyroidism in patients with end-stage renal disease on hemodialysis. *Thyroid.* 2005;15:1321-1331.
- <sup>11</sup>Rao SN, Zaferes M, Dadu R, et al. Patterns of Treatment Failure in Anaplastic Thyroid Carcinoma. *Thyroid.* 2017;27:672-681.
- <sup>12</sup>Heron DE, Karimpour S, Grigsby PW. Anaplastic Thyroid Carcinoma: Comparison of Conventional Radiotherapy and Hyperfractionation Chemoradiotherapy in Two Groups. *Am J Clin Oncol.* 2002;25:442-446.
- <sup>13</sup>Pezzi TA, Mohamed ASR, Sheu T, et al. Radiation Therapy Dose Is Associated With Improved Survival for Unresected Anaplastic Thyroid Carcinoma: Outcomes From the National Cancer Data Base. *Cancer.* 2017;123:1653-1661.
- <sup>14</sup>Park JW, Choi SH, Yoon HI, et al. Treatment Outcomes of Radiotherapy for Anaplastic Thyroid Cancer. *Radiat Oncol J.* 2018;36:103-113.
- <sup>15</sup>Romesser PB, Sherman EJ, Shaha AR, et al. External Beam Radiotherapy With or Without Concurrent Chemotherapy in Advanced or Recurrent Non-Anaplastic Non-Medullary Thyroid Cancer. *J Surg Oncol.* 2014;110:375-382.
- <sup>16</sup>Vernat SS, Khalifa J, Sun X, et al. 10-Year Locoregional Control With Postoperative External Beam Radiotherapy in Patients With Locally Advanced High-Risk Non-Anaplastic Thyroid Carcinoma De Novo or at Relapse, a Propensity Score Analysis. *Cancers (Basel).* 2019;11:849.
- <sup>17</sup>Tuttle RM, Rondeau G, Lee NY. A Risk-Adapted Approach to the Use of Radioactive Iodine and External Beam Radiation in the Treatment of Well-Differentiated Thyroid Cancer. *Cancer Control.* 2011;18:89-95.
- <sup>18</sup>Chen PV, Osborne R, Ahn E, et al. Adjuvant External-Beam Radiotherapy in Patients With High-Risk Well-Differentiated Thyroid Cancer. *Ear Nose Throat J.* 2009;88:E01.
- <sup>19</sup>Azrif M, Slevin NJ, Sykes AJ, et al. Patterns of Relapse Following Radiotherapy for Differentiated Thyroid Cancer: Implication for Target Volume Delineation. *Radiother Oncol.* 2008;89:105-113.
- <sup>20</sup>Hu A, Clark J, Payne RJ, et al. Extrathyroidal Extension in Well-Differentiated Thyroid Cancer: Macroscopic vs Microscopic as a Predictor of Outcome. *Arch Otolaryngol Head Neck Surg.* 2007;133:644-649.
- <sup>21</sup>Keum KC, Suh YG, Koom WS, et al. The Role of Postoperative External-Beam Radiotherapy in the Management of Patients With Papillary Thyroid Cancer Invading the Trachea. *Int J Radiat Biol Phys.* 2006;65:474-480.
- <sup>22</sup>Schlumberger M, Challeton C, De Vathaire F, et al. Radioactive Iodine Treatment and External Radiotherapy for Lung and Bone Metastases From Thyroid Carcinoma. *J Nucl Med.* 1996;37:598-605.
- <sup>23</sup>McWilliams RR, Giannini C, Hay ID, et al. Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. *Cancer.* 2003;98:256-362.
- <sup>24</sup>Osborne JR, Kondraciuk JD, Rice SL, et al. Thyroid cancer brain metastases: Survival and genomic characteristics of a large tertiary care cohort. *Clin Nucl Med.* 2019;44:544-549.
- <sup>25</sup>Rao SN, Zaferes M, Dadu R, et al. Patterns of Treatment Failure in Anaplastic Thyroid Carcinoma. *Thyroid.* 2017;27:672-681.
- <sup>26</sup>Heron DE, Karimpour S, Grigsby PW. Anaplastic thyroid carcinoma: comparison of conventional radiotherapy and hyperfractionation chemoradiotherapy in two groups. *Am J Clin Oncol.* 2002;25:442-446.
- <sup>27</sup>Saeed NA, Kelly JR, Deshpande HA, et al. Adjuvant External Beam Radiotherapy for Surgically Resected, Nonmetastatic Anaplastic Thyroid Cancer. *Head Neck.* 2020; Online ahead of print.
- <sup>28</sup>Wang Y, Tsang R, Asa S, et al. Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer.* 2006;107:1786-1792.

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

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



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

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

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

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

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

|          |                           |
|----------|---------------------------|
| <b>M</b> | <b>Distant Metastasis</b> |
| M0       | No distant metastasis     |
| M1       | Distant metastasis        |

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

**Continued**



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

### Table 2. AJCC Prognostic Stage Groups

#### Differentiated

Under 55 years

|                 | T     | N     | M  |
|-----------------|-------|-------|----|
| <b>Stage I</b>  | Any T | Any N | M0 |
| <b>Stage II</b> | Any T | Any N | M1 |

#### Differentiated

55 Years and Older

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

#### Anaplastic

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

#### Histopathologic Type

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

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

[Continued](#)



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

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

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

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

**M Distant Metastasis**

|           |                       |
|-----------|-----------------------|
| <b>M0</b> | No distant metastasis |
| <b>M1</b> | Distant metastasis    |

**Table 2. AJCC Prognostic Stage Groups**

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

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.



**NCCN Categories of Evidence and Consensus**

|                    |                                                                                                          |
|--------------------|----------------------------------------------------------------------------------------------------------|
| <b>Category 1</b>  | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.    |
| <b>Category 2A</b> | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.   |
| <b>Category 2B</b> | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.           |
| <b>Category 3</b>  | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

**NCCN Categories of Preference**

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

All recommendations are considered appropriate.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Discussion

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

### Table of Contents

#### Overview ..... MS-2

Epidemiology ..... MS-2

Literature Search Criteria and Guidelines Update Methodology ..... MS-3

Managing Differentiated Thyroid Carcinoma ..... MS-3

Radiation-Induced Thyroid Carcinoma ..... MS-3

#### Differentiated Thyroid Carcinoma ..... MS-4

Clinical Presentation and Diagnosis ..... MS-4

Initial Workup ..... MS-4

FNA Results ..... MS-6

Recurrence of Differentiated Thyroid Carcinoma ..... MS-8

Prognosis ..... MS-9

Tumor Staging ..... MS-12

Prognostic Scoring Strategies ..... MS-13

Surgical Management of Differentiated Thyroid Carcinoma ..... MS-13

Radioactive Iodine—Diagnostics and Treatment ..... MS-15

Assessment and Management After Initial Treatment ..... MS-18

#### Papillary Thyroid Carcinoma ..... MS-22

Surgical Therapy ..... MS-22

Radioactive Iodine Therapy ..... MS-24

Surveillance and Maintenance ..... MS-24

Recurrent Disease ..... MS-25

Metastatic Disease Not Amenable to RAI Therapy ..... MS-26

#### Follicular Thyroid Carcinoma ..... MS-27

#### Hürthle Cell Carcinoma ..... MS-28

#### Medullary Thyroid Carcinoma ..... MS-29

Nodule Evaluation and Diagnosis ..... MS-29

Staging ..... MS-30

Surgical Management ..... MS-31

Adjuvant RT ..... MS-32

Persistently Increased Calcitonin ..... MS-33

Postoperative Management and Surveillance ..... MS-33

Recurrent or Persistent Disease ..... MS-34

#### Anaplastic Thyroid Carcinoma ..... MS-35

Diagnosis ..... MS-36

Prognosis ..... MS-36

Treatment ..... MS-36

#### References ..... MS-39



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Overview

#### Epidemiology

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the U.S. population for individuals aged 50 years and older having palpable thyroid nodules.<sup>1-3</sup> 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.<sup>2,4</sup> 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.<sup>5,6</sup>

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%.<sup>7</sup> It is estimated that approximately 53,990 new cases of thyroid carcinoma will be diagnosed in the United States in 2018.<sup>8</sup> 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.<sup>8</sup> The disease is also diagnosed more often in white North Americans than in African Americans. The main histologic types of thyroid carcinoma are: 1) differentiated (including papillary, follicular, and Hürthle cell); 2) medullary; and 3) anaplastic, which is an aggressive undifferentiated tumor. Of 63,324 patients diagnosed with thyroid carcinoma from 2011 to 2015, 89.8% had papillary carcinoma, 4.5% had follicular carcinoma, 1.8% had Hürthle cell carcinoma, 1.6% had medullary carcinoma, and 0.8% had anaplastic carcinoma.<sup>7</sup>

Mortality rates for thyroid carcinoma are, in general, very low. Differentiated thyroid carcinomas usually have an excellent prognosis with 10-year survival rates exceeding 90% to 95%.<sup>9</sup> In contrast, anaplastic thyroid carcinoma is almost uniformly lethal. However, since differentiated

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

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.<sup>9</sup> This Discussion text describes the recommendations in the algorithm in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithm. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Literature Search Criteria and Guidelines Update Methodology

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

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

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

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

### Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma can be a challenge, because until recently, few prospective randomized trials of treatment have been done.<sup>32,33</sup> 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.<sup>34</sup> The treatment of choice is surgery, followed by radioactive iodine (RAI) ablation [iodine 131 (<sup>131</sup>I)] in selected patients and thyroxine therapy in most patients.

### Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma.<sup>35</sup> 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.<sup>5</sup> The risk for radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma.<sup>36</sup> 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.<sup>5,6</sup>

Adults have a very small risk of developing thyroid carcinoma after exposure to <sup>131</sup>I.<sup>37</sup> After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary carcinomas after being exposed to <sup>131</sup>I fallout.<sup>38</sup> It became evident that <sup>131</sup>I and other short-lived <sup>131</sup>Is were potent thyroid carcinogens in these children, particularly those younger than 10 years of age when they were exposed.<sup>39</sup> Iodine deficiency increases the risk for radiation-induced thyroid cancer.<sup>40</sup> 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.<sup>41-43</sup> Iodine deficiency is associated with follicular carcinoma and anaplastic carcinomas.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### 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.<sup>1,44,45</sup> Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their diagnosis. About 50% of the malignant nodules are discovered during a routine physical examination, by serendipity on imaging studies, or during surgery for benign disease. The other 50% are often first noticed by the patient, usually as an asymptomatic nodule.<sup>1,44</sup> 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.<sup>11</sup>

#### 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.<sup>3,46-48</sup> The TSH level, ultrasound results, and clinical features are used to determine whether it is 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).<sup>45,49</sup>

FNA with ultrasound guidance is the procedure of choice for evaluating suspicious thyroid nodules.<sup>3,45,50</sup> 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.<sup>51-54</sup> FNA should be considered in patients with normal or elevated TSH, certain ultrasound

features, and clinical findings. FNA of clinically significant or suspicious cervical lymph nodes should also be considered if identified in the ultrasonographic evaluation of the thyroid and neck. Ultrasound features that increase the threshold for FNA are described in the algorithm (see *Sonographic Features in Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). Iodine 123 (<sup>123</sup>I) imaging is recommended in patients with low TSH.

Sonographic (ultrasound) features can be used to predict either benign or malignant thyroid nodules. Suspicious sonographic features include hypoechoic, microcalcifications, infiltrative margins, and nodules that are taller than they are wide in the transverse plane. Ultrasound features associated with a low suspicion of malignancy include isoechoic or hyperechoic solid nodules, mixed solid/cystic nodules, or spongiform nodules without the suspicious features listed above.<sup>47,55-57</sup> Standardized systems for assessing ultrasound features have been created to improve consistency across centers.<sup>56,58</sup> 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.<sup>57</sup> 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;<sup>47,59</sup> however, it may serve an important role in the setting of other concerning features.<sup>60</sup>

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



## NCCN Guidelines Version 2.2020

### Thyroid Carcinoma

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.<sup>55,56,61</sup> 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.<sup>16,62</sup> 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).<sup>4,13,47,63-67</sup> 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.<sup>68</sup> These observations cast doubt on the clinical benefit of diagnosing (and treating) papillary microcarcinoma in these selected groups.<sup>69</sup> Others feel that surgery should be considered for select patients with papillary carcinomas who are 45 years of age or older.<sup>70</sup>

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).<sup>3,49,71</sup> 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.<sup>72</sup> 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).<sup>45,49</sup> 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.<sup>71</sup> Suspicious criteria by ultrasound include increased central hypervascularity, hypoechoic mass, microcalcifications, infiltrative margins, and other features (see *Sonographic Features in Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).<sup>73,74</sup> 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.<sup>74,75</sup> 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.<sup>75</sup> 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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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.<sup>3,76</sup>

Some clinicians, especially in Europe,<sup>77</sup> 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.<sup>3</sup> A study showed that calcitonin screening may be cost effective in the United States.<sup>78</sup> 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.<sup>79</sup>

### FNA Results

Cytologic examination of an FNA specimen is typically categorized as: category I: nondiagnostic or unsatisfactory biopsy; category II: benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis); category III: atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); category IV: follicular neoplasm or suspicious for follicular neoplasm (includes Hürthle cell neoplasm); category V: suspicious for malignancy; or category

VI: malignancy (includes papillary, medullary, anaplastic, or lymphoma). These diagnostic categories for FNA results reflect the 2017 Bethesda System for Reporting Thyroid Cytopathology.<sup>80</sup> 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.<sup>81,82</sup>

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.<sup>83-91</sup> The *BRAF* V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation.<sup>92</sup> Some studies have linked the *BRAF* V600E mutation to poor prognosis, especially when occurring with *TERT* promoter mutation.<sup>93-96</sup> The choice of the precise molecular test depends on the cytology and the clinical question being asked.<sup>97-100</sup> Indeterminate groups include: 1) follicular or Hürthle cell neoplasms; and 2) AUS/FLUS.<sup>101-103</sup> 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).<sup>104,105</sup>

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



## NCCN Guidelines Version 2.2020

# Thyroid Carcinoma

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

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

A minority of panelists expressed concern regarding active surveillance of follicular lesions because they were perceived as potentially pre-malignant lesions with a very low, but unknown, malignant potential if not surgically resected (leading to recommendations for either active surveillance or considering lobectomy in lesions classified as benign by molecular testing). Clinical risk factors, sonographic patterns, and patient preference can help determine whether active surveillance or lobectomy is appropriate for these patients (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Rather than proceeding to immediate surgical resection to obtain a definitive diagnosis for these indeterminate FNA cytology groups (follicular lesions), patients can be followed with active surveillance if the application of a specific molecular diagnostic test (in conjunction with clinical and ultrasound features) results in a predicted risk of malignancy that is comparable to the rate seen in cytologically benign thyroid FNAs (approximately ≤5%). It is important to note that the predictive value of molecular diagnostics may be significantly influenced by the pre-test probability of disease associated with the various FNA cytology groups. Furthermore, in the cytologically indeterminate groups, the risk of malignancy from FNA can vary widely between institutions.<sup>80,112</sup> 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.<sup>105,113</sup>

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of medullary carcinoma.<sup>49</sup> 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.<sup>114</sup> Metastatic renal carcinoma can mimic follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma.<sup>49</sup> Pathology synoptic reports (protocols), such as those from the College of American Pathologists (CAP), are useful for reporting results from examinations of surgical specimens. The CAP protocol was updated in June 2017 and reflects the 8<sup>th</sup> edition AJCC Staging Manual (see *Protocol for the Examination of*



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

*Specimens From Patients With Carcinomas of the Thyroid Gland on the CAP website).<sup>9,115</sup>*

Follicular and Hürthle cell carcinomas are rarely diagnosed by FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.<sup>34,45,81,116</sup> Approximately 15% to 40% of lesions classified as “follicular neoplasm” or “suspicious for follicular neoplasm” are malignant, with risk of malignancy varying by institution, cytopathologist, and whether or not NIFTP is excluded.<sup>117,118</sup> 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.<sup>119</sup> 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).<sup>73,105,120</sup>

In some patients with follicular lesions, serum TSH level and thyroid <sup>123</sup>I or 99m technetium scanning may identify patients with an autonomously functioning or “hot” nodule who often may be spared surgery, because the diagnosis of follicular adenoma (ie, benign) is highly likely.<sup>3,121</sup> 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).<sup>2,3</sup> 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).<sup>74</sup> In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.<sup>122</sup> Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of significant growth.<sup>74</sup> Significant nodule growth is defined as a greater than 50% increase in nodule volume or 20% increase in size of 2 to 3 dimensions.<sup>123</sup> 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.<sup>11</sup> Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.<sup>124,125</sup> 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.<sup>11</sup> Distant metastases were the sites of recurrence in 21% of patients in this cohort, most often



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

(63%) in the lungs alone. Of the patients with distant metastases, 50% died of cancer.<sup>11</sup>

It is important to recognize that the poor outcomes in this study were probably related to the manner in which the recurrence was diagnosed. In the past, disease recurrence was heralded by symptoms or palpable disease on physical examination, reflecting relatively large-volume disease recurrence. However, tools that are highly sensitive for detecting disease (eg, sensitive Tg assays, high-resolution neck ultrasound) appear to have resulted in earlier detection of disease recurrence, which is now often found in the first 2 to 5 years of follow-up.<sup>3,126</sup> 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.<sup>127,128</sup>

### 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.<sup>11,129-131</sup> 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.<sup>11,129-132</sup> 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.<sup>133,134</sup> 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.<sup>135</sup> 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.<sup>136-138</sup> 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.<sup>11,133,139,140</sup> Prognosis is less favorable in men than in women, but the difference is usually small.<sup>11,138</sup> 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.<sup>11</sup> Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.<sup>141</sup>

#### *Familial Syndromes*

Familial, non-medullary carcinoma accounts for about 5% of papillary thyroid carcinomas (PTCs) and, in some cases, may be clinically more aggressive than the sporadic form.<sup>142,143</sup> 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.<sup>144</sup> Other familial syndromes associated with papillary carcinoma are familial adenomatous polyposis,<sup>145</sup>



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands),<sup>146</sup> and Cowden syndrome (multiple hamartomas).<sup>147</sup> 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.<sup>132,148-150</sup> The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, *BRAF* V600E mutation status, and metastases.<sup>93,94,151</sup> For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.<sup>3,152-155</sup> 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](#)).<sup>115</sup> In patients with sporadic medullary carcinoma, a somatic RET oncogene mutation confers an adverse prognosis.<sup>156</sup>

### Histology

Although survival rates with typical papillary carcinoma are quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors.<sup>1</sup> 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.<sup>34,157,158</sup>

NIFTP, formerly known as noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), is characterized by its follicular growth pattern, encapsulation or clear demarcation of the tumor from adjacent tissue with no invasion, and nuclear features of papillary

carcinoma.<sup>159,160</sup> NIFTP tumors have a low risk for adverse outcomes and, therefore, require less aggressive treatment.<sup>160-163</sup> NIFTP was re-classified in 2016 to prevent overtreatment of this indolent tumor type as well as the psychological consequences of a cancer diagnosis on the patient.<sup>159,160</sup> CAP updated its protocols with NIFTP in the June 2017 version.<sup>115</sup>

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

Follicular thyroid carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It usually has a microfollicular histologic pattern. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.<sup>168</sup> 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.<sup>169</sup> FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.<sup>45,116</sup> Therefore, the tumor is often simply referred to as a “follicular neoplasm” by the cytopathologist (see *Nodule Evaluation* in the



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

NCCN Guidelines for Thyroid Carcinoma).<sup>81</sup> 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.<sup>132</sup> The poor prognosis is closely related to older age at the time of diagnosis, advanced tumor stage, and larger tumor size.<sup>11</sup> 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.<sup>11,170</sup>

When Hürthle (oncocytic) cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as Hürthle cell carcinoma. Previously considered a variant of follicular thyroid carcinoma, the World Health Organization (WHO) and AJCC reclassified Hürthle cell carcinoma as a separate entity in 2017.<sup>9,171</sup> Molecular studies suggest that this tumor may be more similar to papillary than to follicular thyroid carcinomas<sup>172,173</sup> and genotyping revealed that mutational, transcriptional, and copy number profiles of Hürthle cell carcinomas were distinct from papillary and follicular carcinomas, best categorizing it as a unique class of thyroid malignancy.<sup>174</sup> 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.<sup>175</sup> 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.<sup>176,177</sup> 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.<sup>178-180</sup> In contrast to papillary or follicular carcinomas,<sup>131</sup>I may be not effective in patients with Hürthle cell carcinoma because fewer Hürthle cell carcinomas concentrate <sup>131</sup>I. In a series of 100 patients with distant metastases, <sup>131</sup>I uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell carcinomas.<sup>178</sup> In the National Cancer Database report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.<sup>181</sup>

### 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.<sup>182</sup> 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.<sup>183,184</sup> 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,<sup>185</sup> which may be the presenting feature and also may be associated with distant metastases.<sup>182</sup> 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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

### *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.<sup>11,187</sup> 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.<sup>11,188</sup>

### *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.<sup>132</sup> An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.<sup>189</sup> The prognostic importance of regional lymph node metastases is controversial.<sup>3</sup> 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).<sup>190</sup> Older patients (>45 years) with papillary carcinoma and lymph node metastases also have decreased survival.<sup>191</sup> A 2012 review by Randolph et al emphasized the correlation between the size and number of metastatic lymph nodes and the risk of recurrence.<sup>192</sup> 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.<sup>193,194</sup> About 50% of these metastases are present at the time of diagnosis.<sup>132</sup> 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.<sup>178,179</sup> 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 <sup>131</sup>I.<sup>178,179,195,196</sup>

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

### *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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

### 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.<sup>130,136,201-203</sup> These strategies include the EORTC, TNM 7<sup>th</sup> 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.<sup>186</sup> 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.<sup>136</sup>

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.<sup>139</sup> This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.<sup>201,204</sup> The AJCC TNM staging approach (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 55 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,<sup>205,206</sup> 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.<sup>130,207</sup>

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.<sup>3,208-211</sup> 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.<sup>212</sup> 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.<sup>213</sup> Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring<sup>138</sup> and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic Cancer Center for low-risk PTCs (MACIS score ≤3.99) had no improvement in survival rates after undergoing procedures more



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

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

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.<sup>215</sup> 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.<sup>215</sup>

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),<sup>3,34,216</sup> because this procedure is associated with improved disease-free survival.<sup>124,140,215,217</sup> Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.<sup>132,214</sup> After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and  $^{131}\text{I}$  therapy)<sup>11</sup> and the highest frequency (11%) of subsequent pulmonary metastases.<sup>218</sup> However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.<sup>41</sup> Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.<sup>11</sup>

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

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).<sup>3,11,182,221-224</sup> 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.<sup>3</sup> 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.<sup>151,225,226</sup>

### **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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

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.<sup>140</sup> 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.<sup>231</sup>

### Surgical Complications

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

### Radioactive Iodine—Diagnostics and Treatment

#### *Diagnostic Total Body Imaging and Thyroid Stunning*

When indicated, diagnostic total body  $^{131}\text{I}$  imaging is recommended (category 2B) after surgery to assess the completeness of thyroidectomy and to assess whether residual disease is present (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma). However, a phenomenon termed “stunning” may occur when imaging doses of  $^{131}\text{I}$  induce follicular cell damage.<sup>240</sup> Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent  $^{131}\text{I}$ .<sup>241</sup>

To avoid or reduce the stunning effect, the following have been suggested: 1) the use of  $^{123}\text{I}$  or small (2 or 3 mCi) doses of  $^{131}\text{I}$ ; and/or 2) a shortened interval ( $\leq 72$  hours) between the diagnostic  $^{131}\text{I}$  dose and the therapy dose. However,  $^{123}\text{I}$  is more expensive and smaller  $^{131}\text{I}$  doses have reduced sensitivity when compared with larger  $^{131}\text{I}$  doses.<sup>240-242</sup> In addition, a large thyroid remnant may obscure detection of residual disease with  $^{131}\text{I}$  imaging. Some experts recommend that diagnostic  $^{131}\text{I}$  imaging be avoided completely with decisions based on the combination of tumor stage and serum Tg.<sup>240</sup> Other experts advocate that whole-body  $^{131}\text{I}$  diagnostic imaging may alter therapy, for example: 1) when unsuspected metastases are identified; or 2) when an unexpectedly large remnant is identified that requires additional surgery or a reduction in RAI dosage to avoid substantial radiation thyroiditis.<sup>3,240,243-245</sup> Thus, NCCN Panel Members disagreed about using diagnostic total body  $^{131}\text{I}$  imaging before postoperative RAI, which is reflected in the category 2B recommendation



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

for imaging.<sup>3,246–248</sup> Note that diagnostic imaging is used less often for patients at low risk.

### **Eligibility for Postoperative Radioactive Iodine (RAI)**

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

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

Postoperative RAI is selectively recommended for patients who are at greater risk for recurrence with any of the following clinical indications such as largest primary tumor 2 to 4 cm, high-risk histology (for papillary carcinoma), lymphatic or vascular invasion, cervical lymph node metastases, macroscopic multifocality (one focus >1 cm), unstimulated postoperative serum Tg (<5–10 ng/mL), or microscopic positive

margins.<sup>3,249,250</sup> However, the NCCN Panel does not routinely recommend RAI for patients with all of the following factors: 1) either unifocal (<2 cm) or multifocal classic papillary microcarcinomas (all foci ≤1 cm) confined to the thyroid; 2) no detectable anti-Tg antibodies; and 3) postoperative unstimulated Tg less than 1 ng/mL. Guidelines from the ATA list very similar indications for postoperative RAI use and also provide specific guidance regarding the safe use of RAI in the outpatient setting.<sup>3,251</sup>

### **Postoperative Administration of RAI**

Studies show decreased recurrence and disease-specific mortality for populations at intermediate or higher risk when postoperative <sup>131</sup>I therapy is administered as part of the initial treatment.<sup>11,131,139,252–254</sup> 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 <sup>131</sup>I ( $P < .001$ ). Moreover, fewer patients developed distant metastases ( $P < .002$ ) after thyroid remnant <sup>131</sup>I ablation than after other forms of postoperative treatment. However, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter.<sup>252</sup> Another study of 21,870 intermediate risk patients with differentiated thyroid cancer found that postoperative RAI improved OS ( $P < .001$ ) and was associated with a 29% reduction in the risk of death after adjustment for demographic and clinical factors (HR, 0.71; 95% CI, 0.62–0.82;  $P < .001$ ).<sup>254</sup> Some studies have found that remnant ablation had less of a therapeutic effect, perhaps because more extensive locoregional surgery had been done.<sup>186</sup>

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



## NCCN Guidelines Version 2.2020

### Thyroid Carcinoma

secondary malignancies, such as leukemia and salivary gland malignancies, has increased in patients with low-risk thyroid cancer (ie, T1N0) who received RAI.<sup>257</sup> Debate continues about ablating the thyroid bed with <sup>131</sup>I after total thyroidectomy.<sup>3,186,252,258</sup> In patients with papillary carcinoma who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates.<sup>224,250,259</sup> A long-term study (n = 1298) found that overall survival is not improved in patients who receive RAI ablation.<sup>260</sup> Reasons favoring remnant ablation include: 1) simplified patient follow-up, because elimination of thyroid bed uptake prevents misinterpretation of it as disease; 2) elimination of normal tissue as a source of Tg production, which facilitates identification of patients who are free of disease and may simplify their care while promoting early identification of those with residual cancer; and 3) elimination of normal tissue, which may eliminate the nidus for continued confounding anti-Tg antibody production. Conversely, others argue that most recurrences can be easily detected with neck ultrasound and that serum Tg levels are often quite low after a total thyroidectomy. Therefore, in patients at low and intermediate risk, the clinical benefit of routine remnant ablation as a requirement for optimal follow-up remains uncertain.

Data suggest that lower doses of RAI are as effective as higher doses—30 versus 100 mCi—for ablation in patients with low-risk thyroid cancer (eg, T1b/T2 [1–4 cm], clinical N0 disease).<sup>32,33</sup> The NCCN Guidelines reflect a more cautious approach to using RAI ablation based on these randomized trials.<sup>261</sup> If RAI ablation is used, the NCCN Guidelines recommend (category 1) 30 mCi of <sup>131</sup>I for RAI ablation in patients at low risk based on these randomized trials. This same ablation dose—30 mCi—may be considered (category 2B) in patients at slightly higher risk (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).<sup>262</sup> 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.<sup>263</sup> The possible benefits of RAI should be weighed with the risk of adverse effects as part of treatment decision-making.<sup>261</sup> Adverse effects may be minimized by using lower doses of RAI.<sup>32</sup>

Historically, the 3 methods of determining <sup>131</sup>I therapy activities (doses) have included: empiric fixed doses, quantitative dosimetry, and upper-bound limits that are set by blood dosimetry.<sup>3,240,243,264,265</sup> Most patients at NCCN Member Institutions receive postoperative RAI based on empiric fixed dosing; a few centers use a combination of blood dosimetry and quantitative lesional dosimetry. In the past, hospitalization was required to administer therapeutic doses of <sup>131</sup>I greater than 30 mCi (1110 MBq). However, hospitalization is no longer necessary in most states, because a change in federal regulations permits the use of much larger <sup>131</sup>I doses in patients who are ambulatory.<sup>264</sup> However, <sup>131</sup>I therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses.

Administration of a fixed dose of <sup>131</sup>I is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of <sup>131</sup>I in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of <sup>131</sup>I. Lymph node metastases may be treated with about 100 to 175 mCi (3700–6475 MBq) of <sup>131</sup>I. Cancer growing through the thyroid capsule (and incompletely resected) is treated with 150 to 200 mCi (5550–7400 MBq). Patients with distant metastases are usually treated with 100 to 200 mCi (3700–7400 MBq) of <sup>131</sup>I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in the elderly and in those with impaired kidney function.<sup>266,267</sup> Diffuse pulmonary metastases that concentrate 50% or



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

### **Post-Treatment $^{131}\text{I}$ Imaging**

When  $^{131}\text{I}$  therapy is given, whole-body  $^{131}\text{I}$  imaging should be performed several days later to document  $^{131}\text{I}$  uptake by the tumor. Post-treatment whole-body  $^{131}\text{I}$  imaging should be done, primarily because up to 25% of images show lesions that may be clinically important, which were not detected by the diagnostic imaging.<sup>264</sup> 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.<sup>272</sup> Post-treatment imaging was most likely to reveal clinically important new information in patients younger than 45 years who had received  $^{131}\text{I}$  therapy in the past. Conversely, in older patients and patients who had not previously received  $^{131}\text{I}$  therapy, post-treatment imaging rarely yielded new information that altered the patient's prognosis.<sup>272</sup>

### **Assessment and Management After Initial Treatment**

Serum Tg determinations, neck ultrasound, and whole-body  $^{131}\text{I}$  imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation.<sup>273</sup> In contrast, neither serum Tg nor whole-body  $^{131}\text{I}$  imaging is specific for thyroid carcinoma in patients who have not undergone thyroidectomy and remnant ablation. When initial ablative therapy has been completed, serum Tg should be measured periodically. Serum Tg can be measured while the patient is taking thyroxine, but the

test is more sensitive when thyroxine has been stopped or when recombinant human TSH (rhTSH) is given to increase the serum TSH.<sup>274,275</sup>

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.<sup>276</sup> About 6% of patients with detectable serum Tg levels (which are <2 ng/mL after stimulation) will have recurrences over the next 3 to 5 years, whereas only about 2% of patients with completely undetectable serum Tg after stimulation will have recurrences over the next 3 to 5 years. The long-term clinical significance is uncertain for disease only detected by minimally elevated Tg levels after stimulation.

### **Recombinant Human TSH**

During follow-up, periodic withdrawal of thyroid hormone therapy has traditionally been used to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements with (or without)  $^{131}\text{I}$  imaging could be performed to detect residual thyroid tissue or carcinoma. However, patients dislike thyroid hormone withdrawal, because it causes symptomatic hypothyroidism. An alternative to thyroid hormone withdrawal is the administration of rhTSH intramuscularly, which stimulates thyroidal  $^{131}\text{I}$  uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.<sup>277</sup> Administration of rhTSH is well tolerated; nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.<sup>275</sup> It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.<sup>277</sup>

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

compared with imaging and Tg levels obtained after thyroid hormone withdrawal.<sup>275</sup> Data showed that the combination of rhTSH–stimulated whole-body imaging and serum Tg measurements detected 100% of metastatic carcinoma.<sup>275</sup> In this study, 0.9 mg of rhTSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of <sup>131</sup>I on the third day. Whole-body imaging and Tg measurements were performed on the fifth day. Whole-body <sup>131</sup>I images were acquired after 30 minutes of imaging or after obtaining 140,000 counts, whichever came first. A serum Tg of 2.0 ng/mL or higher, obtained 72 hours after the last rhTSH injection, indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole-body imaging findings.<sup>275,278</sup>

### **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 <sup>131</sup>I imaging.<sup>274–276,279</sup> 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 <sup>131</sup>I imaging stipulate using 4-mCi <sup>131</sup>I doses (based on the trial)<sup>275</sup> 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]).<sup>280,281</sup> 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).<sup>282,283</sup> 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.<sup>280,283,284</sup> 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.<sup>284</sup>

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.<sup>285</sup> In patients with coexistent autoimmune thyroid disease at the time of surgery, anti-Tg antibodies may persist for far longer. In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for up to 20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.<sup>286</sup> Patients with persistently undetectable serum Tg and anti-Tg antibody levels have longer disease-free survival when compared with patients who have detectable levels.<sup>287</sup>

### **Treating Patients with Positive Tg and Negative Imaging**

Post-treatment <sup>131</sup>I imaging may indicate the location of metastases when the serum Tg level is increased, but a tumor [or metastases] cannot be found by physical examination or other localizing techniques such as diagnostic <sup>131</sup>I imaging, neck ultrasonography, CT, MRI, or PET.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

Unfortunately, most patients who are diagnostic imaging-negative and Tg-positive are not rendered disease free by  $^{131}\text{I}$  therapy; however, the tumor burden may be diminished.<sup>290</sup> Thus, most patients with residual or recurrent disease confined to the neck undergo re-operation rather than RAI therapy in the hopes of a cure. RAI therapy is more commonly considered for those with distant metastases or inoperable local disease. Patients not benefiting from this therapy can be considered for clinical trials, especially those patients with progressive metastatic disease. When a large tumor is not visible on diagnostic whole-body imaging, its ability to concentrate  $^{131}\text{I}$  is very low; thus, the tumor will not respond to  $^{131}\text{I}$  therapy.

### ***Thyroid Hormone Suppression of TSH***

The use of postoperative levothyroxine to decrease TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma, because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium.<sup>3,243,291,292</sup> 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.<sup>3,293</sup> 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.<sup>294,295</sup>

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated with thyroid hormone suppressive therapy.<sup>11,252,255,292,296-298</sup> 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).<sup>298</sup> 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.<sup>255</sup> 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).<sup>299-301</sup> 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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

involvement (N1).<sup>302</sup> 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.<sup>131</sup> 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%).<sup>303</sup>

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

### **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.<sup>309,310</sup> Brain metastases pose a special problem, because <sup>131</sup>I therapy may induce cerebral edema. Neurosurgical resection can be considered for brain metastases. For solitary brain lesions, either neurosurgical resection

or stereotactic radiosurgery is preferred over whole brain radiation.<sup>311,312</sup> 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.<sup>313</sup> Most recurrent tumors respond well to surgery;<sup>131</sup>I therapy; EBRT, SBRT, or IMRT; or other local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA).<sup>3,314</sup>

### **Systemic Therapy**

Systemic therapy can be considered for tumors that are not surgically resectable; are not responsive to <sup>131</sup>I; are not amenable to EBRT treatment, SBRT, IMRT, or other local therapies; and have clinically significant structural disease progression during the last 6 to 12 months. Among 49 patients with metastatic differentiated thyroid carcinoma who were treated with 5 chemotherapy protocols, only 2 (3%) patients had objective responses.<sup>315</sup> In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.<sup>316</sup> Combination chemotherapy is not clearly superior to doxorubicin therapy alone.<sup>132</sup> Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease.<sup>317</sup> Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.<sup>318-325</sup> Agents include multitargeted kinase inhibitors, such as lenvatinib,<sup>318,321,326-332</sup> sorafenib,<sup>333-340</sup> sunitinib,<sup>338,341,342</sup> axitinib,<sup>343-345</sup> everolimus,<sup>346,347</sup> vandetanib,<sup>348</sup> cabozantinib,<sup>319,349</sup> and pazopanib.<sup>350</sup> BRAF V600E mutant inhibitors, such as vemurafenib and dabrafenib;<sup>351-354</sup> and tropomyosin receptor kinase (TRK) inhibitors, such as larotrectinib.<sup>355</sup> Data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in patients with papillary carcinoma who have ALK gene fusion.<sup>356-359</sup>



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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.<sup>321,329,338,350,360-362</sup> 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.<sup>328,329,363-368</sup> Dose modifications of kinase inhibitors may be required. Pazopanib has been reported to cause reversible hypopigmentation.<sup>369</sup>

## 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.<sup>370</sup> 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.<sup>371</sup> Surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients.<sup>372</sup> In more than 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects.<sup>373</sup> Preoperative ultrasound findings altered the operation in more than 40% of cases. In another report,<sup>374</sup> operative management was altered in 23% of the total group due to findings on the preoperative ultrasound. These studies indicate that preoperative

ultrasound has a high sensitivity for nodal disease and will detect nonpalpable nodal metastases in 20% to 33% of patients, and ultrasound should alter the index operation in a similar percentage of patients. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases, particularly if cytology is negative. Cross-sectional imaging (CT or MRI) should be performed if the thyroid lesion is fixed, bulky, or substernal. Iodinated contrast is required for optimal cervical imaging with CT, although iodinated contrast will delay treatment with RAI. Evaluation of vocal cord mobility may be considered for patients with abnormal voice, a surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Vocal cord mobility may be evaluated by ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy.<sup>375</sup>

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).<sup>3,376,377</sup> 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.<sup>378</sup> 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



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

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.<sup>379</sup> 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.<sup>213</sup> 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.<sup>380</sup> 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.<sup>381</sup> However, most guidelines (eg, NCCN, ATA) do not

recommend active surveillance for patients with PTC.<sup>3</sup> 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.<sup>255</sup> 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.<sup>382</sup> For patients at lower risk who undergo lobectomy plus isthmusectomy, completion of thyroidectomy is recommended for any one of the following risk factors: large tumor (>4 cm), positive resection margins, gross extrathyroidal extension, macroscopic multifocal disease, vascular invasion, or macroscopic nodal metastases. While a retrospective study using the National Cancer Database has shown that a sizable percentage of patients with differentiated thyroid cancer receive RAI therapy following lobectomy,<sup>383</sup> the panel does not support this practice due to a lack of data showing benefit. Therefore, RAI is not recommended following lobectomy for differentiated thyroid cancer.

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Radioactive Iodine Therapy

Postoperative RAI administration is recommended when a number of clinical factors predict a significant risk of recurrence, distant metastases, or disease-specific mortality. Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Algorithms can assist in decision-making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI is not recommended after lobectomy; 3) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 4) RAI is often used for patients with known or suspected distant metastatic disease at presentation. However, some patients may have metastatic disease that may not be amenable to RAI therapy, which is also known as iodine-refractory disease (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).

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.<sup>270</sup> 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).<sup>3,305,306,384-386</sup>

### 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).<sup>3</sup> About 85% of patients are considered

to be low risk after surgery for papillary thyroid cancer.<sup>3</sup> 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.<sup>3</sup> Patients treated with <sup>131</sup>I ablation may be followed with unstimulated Tg annually and with periodic neck ultrasound if they have negative ultrasounds, stimulated Tg less than 2 ng/mL (with negative anti-Tg antibodies), and negative RAI imaging (if performed). However, if they have a clinical suggestion of recurrent disease, then TSH-stimulated testing (or other imaging) may be considered. A subgroup of patients at low risk (eg, micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic neck ultrasound follow-up (without stimulated Tg or follow-up whole-body imaging) as long as their basal Tg remains low (see *Surveillance and Maintenance* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.<sup>3</sup> Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.<sup>3</sup>

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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).<sup>3</sup>

### 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.<sup>3</sup> Cross-sectional imaging with CT or MRI may also be valuable for evaluation and surgical planning, especially when reliable high-resolution diagnostic ultrasound is unavailable and/or there is suspicion of invasion into the aerodigestive tract. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases, particularly if cytology is negative.

Clinically significant nodal recurrence in a previously undissected nodal basin should be treated with a formal compartmental resection.<sup>3</sup> In the central neck, this is usually achieved through a unilateral level VI dissection and, occasionally, a level VII dissection. In the lateral compartment, a formal modified radical neck dissection—including levels II, III, IV, and Vb—should be performed. Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Selective dissection of individual nodal metastases (cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field, and is not recommended in the NCCN Guidelines for

Thyroid Carcinoma. Clinically significant nodal recurrence detected in a previously dissected nodal basin may be treated with a more focused dissection of the region containing the metastatic disease. For example, a level II recurrence detected in a patient who underwent a modified radical neck dissection as part of the primary treatment may only require selective dissection of level II. Likewise, a central neck recurrence detected in a patient who underwent a central neck dissection as part of the primary treatment may only require a focused resection of the region of recurrence.

For unresectable locoregional recurrence, RAI treatment and EBRT or IMRT are recommended if the  $^{131}\text{I}$  imaging is positive.<sup>296,372</sup> Local therapies, such as ethanol ablation or RFA, are also an option if available. EBRT or IMRT alone is another option in the absence of  $^{131}\text{I}$  uptake for select patients not responsive to other therapies.<sup>306,387</sup> When recurrent disease is suspected based on high serum-stimulated Tg values ( $>10$  ng/mL) and negative imaging studies (including PET scans), RAI therapy can be considered using an empiric fixed dose of 100 to 150 mCi of  $^{131}\text{I}$  (see *Recurrent Disease* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). The NCCN Panel had a major disagreement about recommending (category 3) post-treatment  $^{131}\text{I}$  imaging in this setting, because some do not feel that these patients should have imaging. No study has shown a decrease in morbidity or mortality in patients treated with  $^{131}\text{I}$  on the basis of increased Tg measurements alone. In a long-term follow-up study, no survival advantage was associated with empiric high-dose RAI in patients with negative imaging.<sup>388</sup> 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.<sup>389,390</sup> Active surveillance may be considered for patients with low-volume disease that is stable and distant from critical structures.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### 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).<sup>3,391</sup>

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.<sup>309,310,392-394</sup> 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.<sup>395-397</sup> Embolization (or other interventional procedures) of metastases can also be considered either prior to resection or as an alternative to resection.<sup>392,398</sup>

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

For clinically progressive or symptomatic disease, recommended treatment options that could be considered include: 1) lenvatinib (preferred) or sorafenib;<sup>328,333</sup> 2) clinical trials; 3) other small molecule kinase inhibitors if a clinical trial is not available; or 4) resection of distant metastases and/or EBRT or IMRT.<sup>399,400</sup> The recommendations for lenvatinib (preferred) or sorafenib are based on phase 3 randomized trials.<sup>328,333</sup> 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.<sup>326,328,333</sup> 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.<sup>329,330</sup>

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

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

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

### 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.<sup>45,404</sup> Unlike PTC, FNA is not specific for follicular thyroid carcinoma and accounts for the main differences in management of the 2 tumor types.<sup>74,81,116,405</sup> The FNA cytologic diagnosis of “[suspicious for] follicular neoplasm” will prove to be a benign follicular adenoma in 80% of cases. However, 20% of patients with follicular neoplasms on FNA are ultimately diagnosed with follicular thyroid carcinoma when the final pathology is assessed. Molecular diagnostic testing may be useful to determine the status of follicular lesions or lesions of indeterminate significance (including follicular neoplasms, AUS, or FLUS) as more or less likely to be malignant based on the genetic profile. Further diagnostic and treatment decisions for patients who present with follicular neoplasms are based on their TSH levels (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Because most patients with follicular neoplasms on FNA actually have benign disease, total thyroidectomy is recommended only if invasive cancer or metastatic disease is apparent at the time of surgery or if the

patient opts for total thyroidectomy to avoid a second procedure (ie, completion thyroidectomy) if cancer is found at pathologic review.<sup>404,406</sup> 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.<sup>407</sup> Minimally invasive cancers, as well as NIFTP tumors, may also be simply followed carefully, because minimally invasive follicular carcinomas and NIFTP usually have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma do occasionally occur. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see *Recurrent Disease* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

The other features of management and follow-up for follicular thyroid carcinoma are similar to those of PTC. Clinicopathologic factors can be used to guide decisions about whether to administer initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). The NCCN Guidelines provide algorithms to assist in decision-making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

RAI ablation may be used to destroy residual thyroid tissue for suspected or proven thyroid bed uptake; alternatively, patients fitting these criteria may be followed without RAI ablation. Iodine 131 ablation and post-treatment imaging (with consideration of dosimetry for distant metastasis) are recommended for suspected or proven  $^{131}\text{I}$ -avid metastatic foci (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). The decision to perform diagnostic whole-body  $^{131}\text{I}$  imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before  $^{131}\text{I}$  therapy is administered is a category 2B recommendation for both follicular thyroid carcinoma and PTC because of the problem of stunning (see section on *Diagnostic Total Body Imaging and Thyroid Stunning* in this Discussion).

### Hürthle Cell Carcinoma

This tumor (also known as oxyphilic cell carcinoma) is usually assumed to be a variant of follicular thyroid carcinoma,<sup>202,408</sup> although the prognosis of Hürthle cell carcinoma is worse.<sup>177,404,406,409,410</sup> Molecular diagnostic testing may not perform well for Hürthle cell neoplasm as discussed in *FNA Results*, above. The Hürthle cell variant of PTC is rare and seems to have a prognosis similar to follicular carcinoma.<sup>411</sup>

The management of Hürthle cell carcinoma is almost identical to follicular thyroid carcinoma, except that 1) locoregional nodal metastases may be more common, and therefore therapeutic lymph node dissections of the affected compartment may be needed for clinically apparent biopsy-proven disease; and 2) metastatic Hürthle cell tumors are less likely to concentrate  $^{131}\text{I}$  (see *Papillary Thyroid Cancer: Surgical Therapy* in this Discussion).<sup>412</sup> Postoperative EBRT or IMRT can be considered for: 1) unresectable primary Hürthle cell lesions that do not concentrate  $^{131}\text{I}$  if

disease is threatening vital structures; and 2) unresectable locoregional recurrence (see *Postsurgical Evaluation and Recurrent Disease* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma), similar to the management for follicular thyroid carcinoma.<sup>3</sup>

Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). The NCCN Guidelines provide algorithms to assist in decision-making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle cell [Thyroid] Carcinoma).

RAI therapy has been reported to decrease the risk of locoregional recurrence and is recommended for unresectable disease with positive  $^{131}\text{I}$  imaging. Iodine 131 therapy (100–150 mCi) may be considered after thyroidectomy for patients with stimulated Tg levels of more than 10 ng/mL who have negative scans (including FDG-PET) (see *Recurrent Disease* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma).<sup>177</sup> Pretreatment diagnostic imaging ( $^{123}\text{I}$  or low-dose  $^{131}\text{I}$ ) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) may be considered based on pathology, postoperative Tg, and intraoperative findings (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). However, some NCCN Panel Members did not feel that diagnostic total body imaging should be recommended before  $^{131}\text{I}$  therapy is administered, because the thyroid remnant may interfere with the scan, making this a category 2B recommendation.<sup>3</sup>



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid.<sup>413-416</sup> Sporadic MTC accounts for about 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as: 1) MEN type 2A (MEN2A), which is the most common type; and 2) MEN2B.<sup>417,418</sup> Familial MTC is now viewed as a variant of MEN2A.<sup>413,414,419</sup> Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of the disease tend to present at earlier ages.<sup>413,414</sup> The 5-year relative survival for stages I to III is about 93%, whereas 5-year survival for stage IV is about 28%.<sup>181,202</sup> 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.<sup>420</sup> 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, adrenocorticotrophic hormone [ACTH], calcitonin gene-related peptide [CGRP]). Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms.<sup>421</sup> 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.<sup>422-424</sup> However, routine measurement of the basal serum calcitonin concentration is not recommended by the NCCN Panel for evaluating a patient with nodular thyroid disease because of: 1) the expense of screening all thyroid nodules and only finding a few cases of MTC; 2) the lack of confirmatory pentagastrin stimulation testing; and 3) the resulting need for thyroidectomy in some patients who actually have benign thyroid disease.<sup>425,426</sup> The ATA is equivocal about routine calcitonin measurement.<sup>3</sup>

### 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.<sup>415,416</sup> 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<sup>427</sup> and because pentagastrin is no longer available in the United States. When MEN2A is suspected, the NCCN Guidelines recommend measurement of calcium levels with (or without) serum intact parathyroid hormone levels (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade of life, without gender preference. In patients with MEN2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

All familial forms of MTC and MEN2 are inherited in an autosomal-dominant fashion. Mutations in the *RET* proto-oncogene are found in at least 95% of kindreds with MEN2A and 88% of familial MTC.<sup>415,416,428</sup> The *RET* proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; MEN2B and some familial MTC mutations are found within the intracellular exons 14 to 16.<sup>413,414</sup> 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.<sup>429,430</sup> 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;<sup>431</sup> 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.<sup>432</sup>

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum carcinoembryonic antigen [CEA]) and screening of patients with germline *RET* proto-oncogene mutations for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A). Before surgery for MTC, it is important to diagnose and address coexisting pheochromocytoma to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for

Neuroendocrine Tumors, available at [www.NCCN.org](http://www.NCCN.org)). Pheochromocytoma can be removed using laparoscopic adrenalectomy.<sup>413,414,433</sup> 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.<sup>413,414</sup> 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).<sup>9</sup> The 8<sup>th</sup> edition of the AJCC Cancer Staging Manual separated MTC into its own stand-alone chapter.<sup>9</sup> Many of the studies cited in this Discussion reporting on AJCC-TNM staging have referred to the 5<sup>th</sup> edition of the AJCC-TNM staging<sup>200</sup> and not to the 6<sup>th</sup>, 7<sup>th</sup>, or 8<sup>th</sup> editions.<sup>9,201,202</sup>

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



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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

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

### 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*).<sup>444-447</sup> MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, <sup>131</sup>I imaging cannot be used, and RAI treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, TSH suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levothyroxine dose.<sup>413,414</sup>

Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease, because the possibility of MEN2 should dictate testing for a germline *RET* proto-oncogene mutation for all patients with MTC. Pheochromocytomas should be removed (eg, laparoscopic adrenalectomy) before surgery on the thyroid to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine Tumors, available at [www.NCCN.org](http://www.NCCN.org)). Patients with pheochromocytomas must be treated preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery. Forced hydration and alpha-blockade are necessary to prevent hypotension after the tumor is removed. After institution of alpha-blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is 1 cm or larger or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is less than 1 cm and for unilateral thyroid disease (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).<sup>376,420</sup> 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.<sup>413,414,448</sup> Note that C634 mutations are the most common mutations.<sup>413,414</sup> Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN2B who have codon 883 *RET* mutations, 918 *RET* mutations, or compound heterozygous (V804M +



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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).<sup>413,414,449</sup>

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.<sup>413,414,449,450</sup> 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).<sup>413,414,451,452</sup> Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.<sup>413,414,450,451,453</sup> A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with *RET* mutations for MEN2A; longer follow-up is necessary to determine if these patients are cured.<sup>454</sup>

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.<sup>413,414</sup> A bilateral central neck dissection (level VI) can be considered for all patients with MEN2B. For those patients with MEN2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if patients have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for these patients with primary tumor(s) 1 cm or larger in diameter (>0.5 cm for patients with MEN2B) or for patients with central compartment lymph node metastases (see

*Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

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

### Adjuvant RT

EBRT and IMRT have not been adequately studied as adjuvant therapy in MTC.<sup>307,413,455</sup> 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.<sup>456</sup> 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).<sup>413,414</sup> EBRT or IMRT can also be given to palliate painful or progressing bone metastases.<sup>309,310,394,413,414</sup>



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Persistently Increased Calcitonin

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

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease, 15 patients with MEN2A, and 6 patients with MEN2B), the 5- and 10-year survival rates were 90% and 86%, respectively.<sup>457</sup> 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.<sup>439,458</sup> 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.<sup>459</sup> 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.<sup>460,461</sup> 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.<sup>461</sup>

### Postoperative Management and Surveillance

Calcitonin is very useful for surveillance, because this hormone is only produced in the parafollicular cells. Thus, measurements of serum calcitonin and CEA levels are the cornerstone of postoperative assessment for residual disease (see *Surveillance* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). For patients with a detectable basal calcitonin or elevated CEA level, neck ultrasound is recommended. Patients with undetectable calcitonin levels and normal CEA levels can subsequently be followed with annual measurements of serum markers. Additional studies or more frequent testing can be done for those with significantly rising calcitonin or CEA. Nonetheless, the likelihood of significant residual disease is very low in patients with an undetectable basal calcitonin level in a sensitive assay. If the patient has MEN2, annual screening for pheochromocytoma (MEN2B or MEN2A) and hyperparathyroidism (MEN2A) should also be performed. For some low-risk *RET* mutations (eg, codons 768, 790, 804, or 891), less frequent screening may be appropriate.

Patients with detectable serum markers (ie, calcitonin levels  $\geq 150$  pg/mL) should have contrast-enhanced CT ( $\pm$ 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.<sup>413,414</sup> The NCCN Panel recognizes that many different



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

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.<sup>413,414</sup>

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

### Recurrent or Persistent Disease

Kinase inhibitors may be appropriate for select patients with recurrent or persistent MTC that is not resectable (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Although kinase inhibitors may be recommended for patients with MTC, it is important to note that kinase inhibitors may not be appropriate for patients with stable or slowly progressive indolent disease.<sup>329,462,463</sup> Vandetanib and cabozantinib are oral receptor kinase inhibitors that increase PFS in patients with metastatic MTC.<sup>444,447,464-466</sup>

Vandetanib is a multitargeted kinase inhibitor; it inhibits RET, vascular endothelial growth factor receptor (VEGFR), and endothelial growth factor receptor (EGFR).<sup>444</sup> 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.<sup>444</sup> 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.<sup>445</sup> However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity.<sup>467</sup> 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;  $P < .001$ ).<sup>447</sup> Following long-term follow-up, the median overall survival for patients treated with cabozantinib was 26.6 months compared to 21.1 months for placebo, although this difference was not statistically significant (stratified HR, 0.85; 95% CI, .64–1.12,  $P = .24$ ).<sup>468</sup> Exploratory analyses have suggested that cabozantinib may have a greater clinical benefit for medullary thyroid cancers harboring *RET* M918T or *RAS* mutations, although prospective trials are needed to confirm.<sup>468,469</sup> In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC.<sup>446</sup> 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,<sup>470</sup> the following options can be considered: 1) EBRT or IMRT; 2) vandetanib (category 1); or 3) cabozantinib (category



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

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);<sup>444,466,471</sup> 2) cabozantinib (category 1);<sup>447</sup> 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.<sup>341,472-476</sup> If the patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.<sup>413,477-479</sup> EBRT or IMRT can be used for local symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.<sup>395-397</sup> Best supportive care is also recommended.

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

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

### Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas (ATCs) are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.<sup>486</sup> Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.<sup>487</sup> Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.<sup>129,487</sup> The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.<sup>486,488</sup> 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.<sup>29</sup>

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.<sup>489</sup> 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.<sup>488,490,491</sup> Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

Therefore,  $^{131}\text{I}$  imaging cannot be used and RAI treatment is not effective in these patients with ATC.<sup>488</sup>

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.<sup>492</sup> Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.<sup>407,493</sup> The lungs and pleura are the most common site of distant metastases ( $\leq 90\%$  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.<sup>488</sup> 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.<sup>488</sup> 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.<sup>114,488</sup>

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

### Prognosis

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

### 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.<sup>498,502</sup>



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### Surgery

Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.<sup>486</sup> 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.<sup>498</sup> 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.<sup>497,499,503,504</sup> 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).<sup>455,486,488,501,505-509</sup> Surgical excision or external irradiation should be considered for isolated skeletal metastases. For solitary brain lesions, either neurosurgical resection or radiation therapy is recommended. Once brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months. Enteral nutrition may be useful for some patients who have difficulty swallowing (see *Principles of Nutrition: Management and Supportive Care* in the NCCN Guidelines for Head and Neck Cancer, available at [www.NCCN.org](http://www.NCCN.org)). If enteral feeding is considered, a careful conversation should occur with the patient about their wishes.

### Systemic Therapy

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

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



## NCCN Guidelines Version 2.2020

# Thyroid Carcinoma

approved by the FDA for ATC.<sup>488</sup> Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease.<sup>523-525</sup> If weekly paclitaxel is used, the ATA Guidelines recommend using paclitaxel at 60 to 90 mg/m<sup>2</sup> IV weekly and not the dose previously reported in the study by Ain et al.<sup>488,525</sup>

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

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

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 multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.<sup>342,520,529-536</sup> 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).<sup>520,537</sup>

Multimodality therapy is recommended in patients with locally resectable disease (see *Primary Treatment* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).<sup>488,515,520,538-542</sup> Retrospective studies have reported that patients with ATC who receive trimodal therapy including surgery, radiation, and systemic therapy demonstrate improved survival compared to those who undergo less aggressive treatment approaches.<sup>543,544</sup>

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.<sup>545</sup> 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.<sup>356-359</sup> *BRAF* mutations have been reported in patients with ATC,<sup>492,546-548</sup> supporting the utility of the *BRAF* V600E inhibitor, dabrafenib in combination with the MEK inhibitor, and trametinib for treatment of this disease.<sup>522</sup>



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

### References

1. Mazzaferri EL. Thyroid carcinoma: Papillary and follicular. In: Mazzaferri EL, Samaan N, eds. Endocrine Tumors. Cambridge: Blackwell Scientific Publications 1993:278-333.
2. Hegedus L. Clinical practice. The thyroid nodule. *N Engl J Med* 2004;351:1764-1771. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15496625>.
3. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167-1214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19860577>.
4. Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas. Prevalence by palpation and ultrasonography. *Arch Intern Med* 1994;154:1838-1840. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8053752>.
5. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995;141:259-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7871153>.
6. Schneider AB, Bekerman C, Leland J, et al. Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. *J Clin Endocrinol Metab* 1997;82:4020-4027. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9398706>.
7. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Bethesda, MD: National Cancer Institute; 2018. Available at: [https://seer.cancer.gov/csr/1975\\_2015/](https://seer.cancer.gov/csr/1975_2015/).
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29313949>.
9. Amin MB, Edge SB, Greene F, et al., eds. AJCC Cancer Staging Manual, 8th ed. New York: Springer International Publishing; 2017.
10. Jonklaas J, Nogueras-Gonzalez G, Munsell M, et al. The impact of age and gender on papillary thyroid cancer survival. *J Clin Endocrinol Metab* 2012;97:E878-887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22496497>.
11. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97:418-428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7977430>.
12. Stroup AM, Harrell CJ, Herget KA. Long-term survival in young women: hazards and competing risks after thyroid cancer. *J Cancer Epidemiol* 2012;2012:641372. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23091489>.
13. Ito Y, Higashiyama T, Takamura Y, et al. Long-term follow-up for patients with papillary thyroid carcinoma treated as benign nodules. *Anticancer Res* 2007;27:1039-1043. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17465240>.
14. Li N, Du XL, Reitzel LR, et al. Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: review of incidence trends by socioeconomic status within the surveillance, epidemiology, and end results registry, 1980-2008. *Thyroid* 2013;23:103-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23043274>.
15. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg* 2014;140:317-322. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24557566>.
16. Wilhelm S. Evaluation of thyroid incidentaloma. *Surg Clin North Am* 2014;94:485-497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24857572>.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

17. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* 2006;295:2164-2167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16684987>.
18. Ito Y, Tomoda C, Urano T, et al. Papillary microcarcinoma of the thyroid: how should it be treated? *World J Surg* 2004;28:1115-1121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15490053>.
19. Vergamini LB, Frazier AL, Abrantes FL, et al. Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study. *J Pediatr* 2014;164:1481-1485. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24630354>.
20. Bann DV, Goyal N, Camacho F, Goldenberg D. Increasing incidence of thyroid cancer in the Commonwealth of Pennsylvania. *JAMA Otolaryngol Head Neck Surg* 2014;140:1149-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25170647>.
21. Aschebrook-Kilfoy B, Kaplan EL, Chiu BC, et al. The acceleration in papillary thyroid cancer incidence rates is similar among racial and ethnic groups in the United States. *Ann Surg Oncol* 2013;20:2746-2753. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23504142>.
22. Schneider DF, Elfenbein D, Lloyd RV, et al. Lymph node metastases do not impact survival in follicular variant papillary thyroid cancer. *Ann Surg Oncol* 2015;22:158-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25092163>.
23. Wang TS, Goffredo P, Sosa JA, Roman SA. Papillary thyroid microcarcinoma: an over-treated malignancy? *World J Surg* 2014;38:2297-2303. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24791670>.
24. Aschebrook-Kilfoy B, Grogan RH, Ward MH, et al. Follicular thyroid cancer incidence patterns in the United States, 1980-2009. *Thyroid* 2013;23:1015-1021. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23360496>.
25. Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. *Thyroid* 2011;21:125-134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21186939>.
26. Yu GP, Li JC, Branovan D, et al. Thyroid cancer incidence and survival in the national cancer institute surveillance, epidemiology, and end results race/ethnicity groups. *Thyroid* 2010;20:465-473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20384488>.
27. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. *Cancer* 2009;115:3801-3807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19598221>.
28. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev* 2009;18:784-791. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19240234>.
29. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute; 2017. Available at: [https://seer.cancer.gov/csr/1975\\_2014/](https://seer.cancer.gov/csr/1975_2014/).
30. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011;61:212-236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21685461>.
31. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: [http://www.nlm.nih.gov/bsd/bsd\\_key.html](http://www.nlm.nih.gov/bsd/bsd_key.html). Accessed March 9, 2018.
32. Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012;366:1674-1685. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22551128>.
33. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med*



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

2012;366:1663-1673. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22551127>.

34. Sherman SI. Thyroid carcinoma. Lancet 2003;361:501-511. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12583960>.

35. Pellegriti G, Frasca F, Regalbuto C, et al. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013;2013:965212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23737785>.

36. Wong FL, Ron E, Gierlowski T, Schneider AB. Benign thyroid tumors: general risk factors and their effects on radiation risk estimation. Am J Epidemiol 1996;144:728-733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8857821>.

37. Ron E, Doody MM, Becker DV, et al. Cancer mortality following treatment for adult hyperthyroidism. Cooperative Thyrotoxicosis Therapy Follow-up Study Group. JAMA 1998;280:347-355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9686552>.

38. Tronko MD, Howe GR, Bogdanova TI, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: thyroid cancer in Ukraine detected during first screening. J Natl Cancer Inst 2006;98:897-903. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16818853>.

39. Jacob P, Goulko G, Heidenreich WF, et al. Thyroid cancer risk to children calculated. Nature 1998;392:31-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9510245>.

40. Cardis E, Kesminiene A, Ivanov V, et al. Risk of thyroid cancer after exposure to 131I in childhood. J Natl Cancer Inst 2005;97:724-732. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15900042>.

41. Tuttle RM, Vaisman F, Tronko MD. Clinical presentation and clinical outcomes in Chernobyl-related paediatric thyroid cancers: what do we know now? What can we expect in the future? Clin Oncol (R Coll Radiol)

2011;23:268-275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21324656>.

42. Schneider AB. Radiation-induced thyroid tumors. Endocrinol Metab Clin North Am 1990;19:495-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2261904>.

43. Nikiforov YE, Nikiforova M, Fagin JA. Prevalence of minisatellite and microsatellite instability in radiation-induced post-Chernobyl pediatric thyroid carcinomas. Oncogene 1998;17:1983-1988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9788442>.

44. Kaplan MM. Clinical evaluation and management of solitary thyroid nodules. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:996-1010.

45. Layfield LJ, Cibas ES, Gharib H, Mandel SJ. Thyroid aspiration cytology: current status. CA Cancer J Clin 2009;59:99-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19278960>.

46. Czerwonka L, Freeman J, McIver B, et al. Summary of proceedings of the second World Congress on Thyroid Cancer. Head Neck 2014;36:917-920. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24677329>.

47. Shrestha M, Crothers BA, Burch HB. The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: a 10-year study from a single institution. Thyroid 2012;22:1251-1256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22962940>.

48. Koike E, Noguchi S, Yamashita H, et al. Ultrasonographic characteristics of thyroid nodules: prediction of malignancy. Arch Surg 2001;136:334-337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11231857>.

49. Baloch ZW, Cibas ES, Clark DP, et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal 2008;5:6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18394201>.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

50. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. *Cancer* 2007;111:306-315. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17680588>.
51. Rinaldi S, Plummer M, Biessy C, et al. Thyroid-stimulating hormone, thyroglobulin, and thyroid hormones and risk of differentiated thyroid carcinoma: the EPIC study. *J Natl Cancer Inst* 2014;106:dju097. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24824312>.
52. McLeod DS, Watters KF, Carpenter AD, et al. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. *J Clin Endocrinol Metab* 2012;97:2682-2692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22622023>.
53. Jin J, Machekano R, McHenry CR. The utility of preoperative serum thyroid-stimulating hormone level for predicting malignant nodular thyroid disease. *Am J Surg* 2010;199:294-297; discussion 298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20226898>.
54. Haymart MR, Repplinger DJ, Leverson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab* 2008;93:809-814. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18160464>.
55. Bonavita JA, Mayo J, Babb J, et al. Pattern recognition of benign nodules at ultrasound of the thyroid: which nodules can be left alone? *AJR Am J Roentgenol* 2009;193:207-213. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19542415>.
56. Friedrich-Rust M, Meyer G, Dauth N, et al. Interobserver agreement of Thyroid Imaging Reporting and Data System (TIRADS) and strain elastography for the assessment of thyroid nodules. *PLoS One* 2013;8:e77927. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24205031>.
57. Alexander EK, Cooper D. The importance, and important limitations, of ultrasound imaging for evaluating thyroid nodules. *JAMA Intern Med* 2013;173:1796-1797. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23979653>.
58. Horvath E, Majlis S, Rossi R, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. *J Clin Endocrinol Metab* 2009;94:1748-1751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19276237>.
59. Kamran SC, Marqusee E, Kim MI, et al. Thyroid nodule size and prediction of cancer. *J Clin Endocrinol Metab* 2013;98:564-570. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23275525>.
60. Smith-Bindman R, Lebda P, Feldstein VA, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. *JAMA Intern Med* 2013;173:1788-1796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23978950>.
61. Yoo WS, Choi HS, Cho SW, et al. The role of ultrasound findings in the management of thyroid nodules with atypia or follicular lesions of undetermined significance. *Clin Endocrinol (Oxf)* 2014;80:735-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24117478>.
62. Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. *J Clin Endocrinol Metab* 2012;97:3866-3875. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22904176>.
63. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 2010;34:28-35. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20020290>.
64. Neuhold N, Schultheis A, Hermann M, et al. Incidental papillary microcarcinoma of the thyroid--further evidence of a very low malignant potential: a retrospective clinicopathological study with up to 30 years of follow-up. *Ann Surg Oncol* 2011;18:3430-3436. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21431405>.
65. Takami H, Ito Y, Okamoto T, et al. Revisiting the guidelines issued by the Japanese Society of Thyroid Surgeons and Japan Association of



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

Endocrine Surgeons: a gradual move towards consensus between Japanese and western practice in the management of thyroid carcinoma. *World J Surg* 2014;38:2002-2010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24671301>.

66. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid* 2003;13:381-387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12804106>.

67. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med* 1997;126:226-231. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9027275>.

68. Ito Y, Miyauchi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* 2014;24:27-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24001104>.

69. Kim HJ, Kim NK, Choi JH, et al. Radioactive iodine ablation does not prevent recurrences in patients with papillary thyroid microcarcinoma. *Clin Endocrinol (Oxf)* 2013;78:614-620. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22957654>.

70. Nilubol N, Kebebew E. Should small papillary thyroid cancer be observed? A population-based study. *Cancer* 2015;121:1017-1024. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25425528>.

71. Frates MC, Benson CB, Charboneau JW, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. *Radiology* 2005;237:794-800. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16304103>.

72. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated

Thyroid Cancer. *Thyroid* 2016;26:1-133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26462967>.

73. Bomeli SR, LeBeau SO, Ferris RL. Evaluation of a thyroid nodule. *Otolaryngol Clin North Am* 2010;43:229-238, vii. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20510711>.

74. Mazzaferri EL. Thyroid cancer in thyroid nodules: finding a needle in the haystack. *Am J Med* 1992;93:359-362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1415298>.

75. Hamming JF, Goslings BM, van Steenis GJ, et al. The value of fine-needle aspiration biopsy in patients with nodular thyroid disease divided into groups of suspicion of malignant neoplasms on clinical grounds. *Arch Intern Med* 1990;150:113-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2297281>.

76. Chan BK, Desser TS, McDougall IR, et al. Common and uncommon sonographic features of papillary thyroid carcinoma. *J Ultrasound Med* 2003;22:1083-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14606565>.

77. Henry JF, Denizot A, Puccini M, et al. [Early diagnosis of sporadic medullary cancers of the thyroid: value of systematic assay of calcitonin]. *Presse Med* 1996;25:1583-1588. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8952672>.

78. Cheung K, Roman SA, Wang TS, et al. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. *J Clin Endocrinol Metab* 2008;93:2173-2180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18364376>.

79. Doyle P, Duren C, Nerlich K, et al. Potency and tolerance of calcitonin stimulation with high-dose calcium versus pentagastrin in normal adults. *J Clin Endocrinol Metab* 2009;94:2970-2974. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19491231>.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

80. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 2017;27:1341-1346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29091573>.
81. Eilers SG, LaPolice P, Mukunyadzi P, et al. Thyroid fine-needle aspiration cytology: performance data of neoplastic and malignant cases as identified from 1558 responses in the ASCP Non-GYN Assessment program thyroid fine-needle performance data. *Cancer Cytopathol* 2014;122:745-750. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24913410>.
82. Yeh MW, Demircan O, Ituarte P, Clark OH. False-negative fine-needle aspiration cytology results delay treatment and adversely affect outcome in patients with thyroid carcinoma. *Thyroid* 2004;14:207-215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15072703>.
83. Giordano TJ, Beaudenon-Huibregtse S, Shinde R, et al. Molecular testing for oncogenic gene mutations in thyroid lesions: a case-control validation study in 413 postsurgical specimens. *Hum Pathol* 2014;45:1339-1347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24830619>.
84. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med* 2012;367:705-715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22731672>.
85. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *J Clin Endocrinol Metab* 2011;96:3390-3397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21880806>.
86. Ohori NP, Nikiforova MN, Schoedel KE, et al. Contribution of molecular testing to thyroid fine-needle aspiration cytology of "follicular lesion of undetermined significance/atypia of undetermined significance". *Cancer Cytopathol* 2010;118:17-23. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20099311>.
87. Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct BRAF and RAS mutation patterns. *Mod Pathol* 2010;23:1191-1200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20526288>.
88. Nikiforov YE, Steward DL, Robinson-Smith TM, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. *J Clin Endocrinol Metab* 2009;94:2092-2098. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19318445>.
89. Musholt TJ, Fottner C, Weber MM, et al. Detection of papillary thyroid carcinoma by analysis of BRAF and RET/PTC1 mutations in fine-needle aspiration biopsies of thyroid nodules. *World J Surg* 2010;34:2595-2603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20652698>.
90. Lassalle S, Hofman V, Ilie M, et al. Clinical impact of the detection of BRAF mutations in thyroid pathology: potential usefulness as diagnostic, prognostic and theragnostic applications. *Curr Med Chem* 2010;17:1839-1850. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20345340>.
91. Chudova D, Wilde JI, Wang ET, et al. Molecular classification of thyroid nodules using high-dimensionality genomic data. *J Clin Endocrinol Metab* 2010;95:5296-5304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20826580>.
92. Yarchoan M, LiVolsi VA, Brose MS. BRAF mutation and thyroid cancer recurrence. *J Clin Oncol* 2015;33:7-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25422487>.
93. Li C, Lee KC, Schneider EB, Zeiger MA. BRAF V600E mutation and its association with clinicopathological features of papillary thyroid cancer: a meta-analysis. *J Clin Endocrinol Metab* 2012;97:4559-4570. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23055546>.
94. Basolo F, Torregrossa L, Giannini R, et al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. *J Clin*



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

Endocrinol Metab 2010;95:4197-4205. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20631031>.

95. Liu R, Bishop J, Zhu G, et al. Mortality Risk Stratification by Combining BRAF V600E and TERT Promoter Mutations in Papillary Thyroid Cancer: Genetic Duet of BRAF and TERT Promoter Mutations in Thyroid Cancer Mortality. JAMA Oncol 2016. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/27581851>.

96. Vuong HG, Altibi AMA, Duong UNP, Hassell L. Prognostic implication of BRAF and TERT promoter mutation combination in papillary thyroid carcinoma-A meta-analysis. Clin Endocrinol (Oxf) 2017;87:411-417. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28666074>.

97. Sadow PM, Heinrich MC, Corless CL, et al. Absence of BRAF, NRAS, KRAS, HRAS mutations, and RET/PTC gene rearrangements distinguishes dominant nodules in Hashimoto thyroiditis from papillary thyroid carcinomas. Endocr Pathol 2010;21:73-79. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20012784>.

98. Rodrigues HG, AA DEP, Adan LF. Contribution of the BRAF oncogene in the pre-operative phase of thyroid carcinoma. Oncol Lett 2013;6:191-196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23946802>.

99. Canadas-Garre M, Becerra-Massare P, Lopez de la Torre-Casares M, et al. Reduction of false-negative papillary thyroid carcinomas by the routine analysis of BRAF(T1799A) mutation on fine-needle aspiration biopsy specimens: a prospective study of 814 thyroid FNAB patients. Ann Surg 2012;255:986-992. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22504197>.

100. Lee ST, Kim SW, Ki CS, et al. Clinical implication of highly sensitive detection of the BRAF V600E mutation in fine-needle aspirations of thyroid nodules: a comparative analysis of three molecular assays in 4585 consecutive cases in a BRAF V600E mutation-prevalent area. J Clin Endocrinol Metab 2012;97:2299-2306. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22500044>.

101. Kleiman DA, Sporn MJ, Beninato T, et al. Preoperative BRAF(V600E) mutation screening is unlikely to alter initial surgical treatment of patients with indeterminate thyroid nodules: a prospective case series of 960 patients. Cancer 2013;119:1495-1502. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23280049>.

102. McIver B, Castro MR, Morris JC, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab 2014;99:4069-4077. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24780044>.

103. Kloos RT, Reynolds JD, Walsh PS, et al. Does addition of BRAF V600E mutation testing modify sensitivity or specificity of the Afirma Gene Expression Classifier in cytologically indeterminate thyroid nodules? J Clin Endocrinol Metab 2013;98:E761-768. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23476074>.

104. Theoharis C, Roman S, Sosa JA. The molecular diagnosis and management of thyroid neoplasms. Curr Opin Oncol 2012;24:35-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22123232>.

105. Hodak SP, Rosenthal DS, American Thyroid Association Clinical Affairs C. Information for clinicians: commercially available molecular diagnosis testing in the evaluation of thyroid nodule fine-needle aspiration specimens. Thyroid 2013;23:131-134. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22984796>.

106. Celik B, Whetsell CR, Nassar A. Afirma GEC and thyroid lesions: An institutional experience. Diagn Cytopathol 2015;43:966-970. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26466552>.

107. Brauner E, Holmes BJ, Krane JF, et al. Performance of the Afirma Gene Expression Classifier in Hurthle Cell Thyroid Nodules Differs from Other Indeterminate Thyroid Nodules. Thyroid 2015;25:789-796. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25962906>.

108. Duh Q, Angell TE, Babiarcz J, et al. Development and validation of classifiers to enhance the Afirma genomic sequencing classifier performance among Hürthle cell specimens [abstract]. Thyroid 2017;27:



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

suppl 1. Available at:

<https://www.liebertpub.com/doi/pdf/10.1089/thy.2017.29050.sc.abstracts>.

109. Nikiforova MN, Mercurio S, Wald AI, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer* 2018;124:1682-1690. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/29345728>.

110. Duick DS, Klopper JP, Diggans JC, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. *Thyroid* 2012;22:996-1001. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22873825>.

111. Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. *J Clin Endocrinol Metab* 2014;99:119-125. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24152684>.

112. Wang CC, Friedman L, Kennedy GC, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. *Thyroid* 2011;21:243-251. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/21190442>.

113. Albarel F, Conte-Devolx B, Oliver C. From nodule to differentiated thyroid carcinoma: contributions of molecular analysis in 2012. *Ann Endocrinol (Paris)* 2012;73:155-164. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22503804>.

114. Asa SL, Bedard YC. Fine-needle aspiration cytology and histopathology. In: Clark OH, Noguchi S, eds. *Thyroid Cancer: Diagnosis and Treatment*. St Louis: Quality Medical Publishing; 2000:105-126.

115. Seethala RR, Asa SL, Bullock MJ, et al. Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland. Protocol web posting date: June 2017: College of American Pathologists; 2017. Available at: <https://cap.objects.frb.io/protocols/cp-thyroid-17protocol-4000.pdf>.

116. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of "follicular neoplasm": a gray zone in thyroid fine-needle aspiration cytology. *Diagn Cytopathol* 2002;26:41-44. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/11782086>.

117. Baloch ZW, Seethala RR, Faquin WC, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTN): A changing paradigm in thyroid surgical pathology and implications for thyroid cytopathology. *Cancer Cytopathol* 2016;124:616-620. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/27203786>.

118. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in The Bethesda System for Reporting Thyroid Cytopathology. *Cancer Cytopathol* 2016;124:181-187. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26457584>.

119. Horne MJ, Chhieng DC, Theoharis C, et al. Thyroid follicular lesion of undetermined significance: Evaluation of the risk of malignancy using the two-tier sub-classification. *Diagn Cytopathol* 2012;40:410-415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22508675>.

120. Moses W, Weng J, Sansano I, et al. Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. *World J Surg* 2010;34:2589-2594. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20703476>.

121. Cersosimo E, Gharib H, Suman VJ, Goellner JR. "Suspicious" thyroid cytologic findings: outcome in patients without immediate surgical treatment. *Mayo Clin Proc* 1993;68:343-348. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8455392>.

122. McHenry CR, Walfish PG, Rosen IB. Non-diagnostic fine needle aspiration biopsy: a dilemma in management of nodular thyroid disease. *Am Surg* 1993;59:415-419. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8323073>.

123. Brauer VF, Eder P, Miehle K, et al. Interobserver variation for ultrasound determination of thyroid nodule volumes. *Thyroid*



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

2005;15:1169-1175. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16279851>.

124. Newman KD, Black T, Heller G, et al. Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. Ann Surg 1998;227:533-541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9563542>.

125. Robie DK, Dinauer CW, Tuttle RM, et al. The impact of initial surgical management on outcome in young patients with differentiated thyroid cancer. J Pediatr Surg 1998;33:1134-1138; discussion 1139-1140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9694109>.

126. Leenhardt L, Erdogan MF, Hegedus L, et al. 2013 European thyroid association guidelines for cervical ultrasound scan and ultrasound-guided techniques in the postoperative management of patients with thyroid cancer. Eur Thyroid J 2013;2:147-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24847448>.

127. Robenshtok E, Fish S, Bach A, et al. Suspicious cervical lymph nodes detected after thyroidectomy for papillary thyroid cancer usually remain stable over years in properly selected patients. J Clin Endocrinol Metab 2012;97:2706-2713. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22639292>.

128. Rondeau G, Fish S, Hann LE, et al. Ultrasonographically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression. Thyroid 2011;21:845-853. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21809914>.

129. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. Cancer 1997;79:564-573. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9028369>.

130. Sherman SI, Brierley JD, Sperling M, et al. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer 1998;83:1012-1021. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9731906>.

131. Tsang RW, Brierley JD, Simpson WJ, et al. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 1998;82:375-388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9445196>.

132. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993;328:553-559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8426623>.

133. Dottorini ME, Vignati A, Mazzucchelli L, et al. Differentiated thyroid carcinoma in children and adolescents: a 37-year experience in 85 patients. J Nucl Med 1997;38:669-675. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9170425>.

134. Samuel AM, Rajashekharao B, Shah DH. Pulmonary metastases in children and adolescents with well-differentiated thyroid cancer. J Nucl Med 1998;39:1531-1536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9744337>.

135. Schlumberger M, De Vathaire F, Travagli JP, et al. Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J Clin Endocrinol Metab 1987;65:1088-1094. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3680475>.

136. Hay ID, Bergstrahl EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050-1057; discussion 1057-1058. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8256208>.

137. Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery 1995;118:1131-



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

- 1136; discussion 1136-1138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7491533>.
138. Cady B. Staging in thyroid carcinoma. *Cancer* 1998;83:844-847. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9731884>.
139. DeGroot LJ, Kaplan EL, Straus FH, Shukla MS. Does the method of management of papillary thyroid carcinoma make a difference in outcome? *World J Surg* 1994;18:123-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8197768>.
140. Miccoli P, Antonelli A, Spinelli C, et al. Completion total thyroidectomy in children with thyroid cancer secondary to the Chernobyl accident. *Arch Surg* 1998;133:89-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9438766>.
141. Palme CE, Waseem Z, Raza SN, et al. Management and outcome of recurrent well-differentiated thyroid carcinoma. *Arch Otolaryngol Head Neck Surg* 2004;130:819-824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15262757>.
142. Frankenthaler RA, Sellin RV, Cangir A, Goepfert H. Lymph node metastasis from papillary-follicular thyroid carcinoma in young patients. *Am J Surg* 1990;160:341-343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2221231>.
143. Hemminki K, Eng C, Chen B. Familial risks for nonmedullary thyroid cancer. *J Clin Endocrinol Metab* 2005;90:5747-5753. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16030170>.
144. Agostini L, Mazzi P, Cavaliere A. Multiple primary malignant tumours: gemistocytic astrocytoma with leptomeningeal spreading and papillary thyroid carcinoma. A case report. *Acta Neurol (Napoli)* 1990;12:305-310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2251958>.
145. Soravia C, Sugg SL, Berk T, et al. Familial adenomatous polyposis-associated thyroid cancer: a clinical, pathological, and molecular genetics study. *Am J Pathol* 1999;154:127-135. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9916927>.
146. Stratakis CA, Courcoutsakis NA, Abati A, et al. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). *J Clin Endocrinol Metab* 1997;82:2037-2043. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9215269>.
147. Marsh DJ, Dahia PL, Caron S, et al. Germline PTEN mutations in Cowden syndrome-like families. *J Med Genet* 1998;35:881-885. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9832031>.
148. Mazzaferri EL. Papillary thyroid carcinoma: factors influencing prognosis and current therapy. *Semin Oncol* 1987;14:315-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3306936>.
149. LiVolsi VA. Follicular lesions of the thyroid. In: LiVolsi VA, ed. *Surgical Pathology of the Thyroid*. Philadelphia: WB Saunders; 1990:173-212.
150. LiVolsi VA. Papillary lesions of the thyroid. In: LiVolsi VA, ed. *Surgical Pathology of the Thyroid*. Philadelphia: WB Saunders; 1990:136-172.
151. Ghossein R. Update to the College of American Pathologists reporting on thyroid carcinomas. *Head Neck Pathol* 2009;3:86-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20596997>.
152. Gardner RE, Tuttle RM, Burman KD, et al. Prognostic importance of vascular invasion in papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg* 2000;126:309-312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10722002>.
153. Mai KT, Khanna P, Yazdi HM, et al. Differentiated thyroid carcinomas with vascular invasion: a comparative study of follicular, Hurthle cell and papillary thyroid carcinoma. *Pathology* 2002;34:239-244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12109784>.
154. Furlan JC, Bedard YC, Rosen IB. Clinicopathologic significance of histologic vascular invasion in papillary and follicular thyroid carcinomas. *J Am Coll Surg* 2004;198:341-348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14992733>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

155. Falvo L, Catania A, D'Andrea V, et al. Prognostic importance of histologic vascular invasion in papillary thyroid carcinoma. *Ann Surg* 2005;241:640-646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15798466>.
156. Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *J Clin Endocrinol Metab* 2008;93:682-687. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18073307>.
157. LiVolsi VA. Unusual variants of papillary thyroid carcinoma. In: Mazzaferri EL, Kreisberg RA, Bar RS, eds. *Advances in Endocrinology and Metabolism*. St. Louis: Mosby-Year Book; 1994:39-54.
158. Vuong HG, Kondo T, Pham TQ, et al. Prognostic significance of diffuse sclerosing variant papillary thyroid carcinoma: a systematic review and meta-analysis. *Eur J Endocrinol* 2017;176:431-439. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28183787>.
159. Patel KN. Noninvasive Encapsulated Follicular Variant of Papillary Thyroid "Cancer" (or Not): Time for a Name Change. *JAMA Oncol* 2016;2:1005-1006. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27077657>.
160. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. *JAMA Oncol* 2016;2:1023-1029. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27078145>.
161. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. *Thyroid* 2013;23:273-279. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23025507>.
162. Piana S, Frasoldati A, Di Felice E, et al. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. *Am J Surg Pathol* 2010;34:868-872. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20463572>.
163. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. *Cancer* 2006;107:1255-1264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16900519>.
164. Paulson VA, Shivdasani P, Angell TE, et al. NIFTP Accounts for Over Half of "Carcinomas" Harboring RAS Mutations. *Thyroid* 2017. Available at: <http://onlinelibrary.wiley.com/wol1/doi/10.1002/cncy.21830/full>.
165. Brandler TC, Liu CZ, Cho M, et al. Does Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP) Have a Unique Molecular Profile? *Am J Clin Pathol* 2018. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30052723>.
166. Jiang XS, Harrison GP, Datto MB. Young Investigator Challenge: Molecular testing in noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Cancer Cytopathol* 2016;124:893-900. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27893191>.
167. Song SJ, LiVolsi VA, Montone K, Baloch Z. Pre-operative features of non-invasive follicular thyroid neoplasms with papillary-like nuclear features: An analysis of their cytological, Gene Expression Classifier and sonographic findings. *Cytopathology* 2017;28:488-494. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29165886>.
168. van Heerden JA, Hay ID, Goellner JR, et al. Follicular thyroid carcinoma with capsular invasion alone: a nonthreatening malignancy. *Surgery* 1992;112:1130-1136; discussion 1136-1138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1455315>.
169. LiVolsi VA, Asa SL. The demise of follicular carcinoma of the thyroid gland. *Thyroid* 1994;4:233-236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7920009>.
170. Brennan MD, Bergstrahl EJ, van Heerden JA, McConahey WM. Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc* 1991;66:11-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1988751>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

171. Lloyd RV, Osamura RY, Klöppel G, Rosai J, eds. WHO Classification of Tumors of Endocrine Organs. In: Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H, eds. World Health Organization Classification of Tumors (ed 4). Lyon, France: International Agency for Research on Cancer; 2017.
172. Maxwell EL, Palme CE, Freeman J. Hurthle cell tumors: applying molecular markers to define a new management algorithm. *Arch Otolaryngol Head Neck Surg* 2006;132:54-58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16415430>.
173. Belchett G, Cheung CC, Freeman J, et al. Hurthle cell tumors: using molecular techniques to define a novel classification system. *Arch Otolaryngol Head Neck Surg* 2002;128:237-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11886336>.
174. Ganly I, Ricarte Filho J, Eng S, et al. Genomic dissection of Hurthle cell carcinoma reveals a unique class of thyroid malignancy. *J Clin Endocrinol Metab* 2013;98:E962-972. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23543667>.
175. Chen H, Nicol TL, Zeiger MA, et al. Hurthle cell neoplasms of the thyroid: are there factors predictive of malignancy? *Ann Surg* 1998;227:542-546. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9563543>.
176. Thompson NW, Dunn EL, Batsakis JG, Nishiyama RH. Hurthle cell lesions of the thyroid gland. *Surg Gynecol Obstet* 1974;139:555-560. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4479589>.
177. Lopez-Penabad L, Chiu AC, Hoff AO, et al. Prognostic factors in patients with Hurthle cell neoplasms of the thyroid. *Cancer* 2003;97:1186-1194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12599224>.
178. Samaan NA, Schultz PN, Haynie TP, Ordonez NG. Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. *J Clin Endocrinol Metab* 1985;60:376-380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3965495>.
179. Ruegemer JJ, Hay ID, Bergstrahl EJ, et al. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. *J Clin Endocrinol Metab* 1988;67:501-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3410936>.
180. Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. *J Clin Endocrinol Metab* 1992;75:714-720. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1517360>.
181. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see comments]. *Cancer* 1998;83:2638-2648. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9874472>.
182. Baudin E, Travagli JP, Ropers J, et al. Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 1998;83:553-559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9690549>.
183. Roti E, degli Uberti EC, Bondanelli M, Braverman LE. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. *Eur J Endocrinol* 2008;159:659-673. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18713843>.
184. Mazzaferri EL. Management of low-risk differentiated thyroid cancer. *Endocr Pract* 2007;13:498-512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17872353>.
185. Sugino K, Ito K, Jr., Ozaki O, et al. Papillary microcarcinoma of the thyroid. *J Endocrinol Invest* 1998;21:445-448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9766259>.
186. Hay ID. Papillary thyroid carcinoma. *Endocrinol Metab Clin North Am* 1990;19:545-576. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2261906>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

187. Emerick GT, Duh QY, Siperstein AE, et al. Diagnosis, treatment, and outcome of follicular thyroid carcinoma. *Cancer* 1993;72:3287-3295. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8080485>.
188. Salvesen H, Njolstad PR, Akslen LA, et al. Papillary thyroid carcinoma: a multivariate analysis of prognostic factors including an evaluation of the p-TNM staging system. *Eur J Surg* 1992;158:583-589. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1363062>.
189. Pingpank JF, Jr., Sasson AR, Hanlon AL, et al. Tumor above the spinal accessory nerve in papillary thyroid cancer that involves lateral neck nodes: a common occurrence. *Arch Otolaryngol Head Neck Surg* 2002;128:1275-1278. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12431169>.
190. Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg* 2005;71:731-734. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16468507>.
191. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery* 2008;144:1070-1077; discussion 1077-1078. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19041020>.
192. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid* 2012;22:1144-1152. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23083442>.
193. Benbassat CA, Mechlis-Frish S, Hirsch D. Clinicopathological characteristics and long-term outcome in patients with distant metastases from differentiated thyroid cancer. *World J Surg* 2006;30:1088-1095. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16736341>.
194. Sampson E, Brierley JD, Le LW, et al. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. *Cancer* 2007;110:1451-1456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17705176>.
195. Schlumberger M, Challeton C, De Vathaire F, Parmentier C. Treatment of distant metastases of differentiated thyroid carcinoma. *J Endocrinol Invest* 1995;18:170-172. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7629392>.
196. Sisson JC, Giordano TJ, Jamadar DA, et al. 131-I treatment of micronodular pulmonary metastases from papillary thyroid carcinoma. *Cancer* 1996;78:2184-2192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8918413>.
197. Schlumberger M, Challeton C, De Vathaire F, et al. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *J Nucl Med* 1996;37:598-605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8691248>.
198. Brown AP, Greening WP, McCready VR, et al. Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. *Br J Radiol* 1984;57:323-327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6704664>.
199. Casara D, Rubello D, Saladini G, et al. Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. *J Nucl Med* 1993;34:1626-1631. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8410272>.
200. Fleming ID, Cooper JS, Henson DE. AJCC Cancer Staging Manual, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 1997.
201. Greene FL, Page DL, Fleming ID. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; 2002.
202. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010:1-646.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

203. Cady B. Hayes Martin Lecture. Our AMES is true: how an old concept still hits the mark: or, risk group assignment points the arrow to rational therapy selection in differentiated thyroid cancer. *Am J Surg* 1997;174:462-468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9374215>.
204. Cady B, Sedgwick CE, Meissner WA, et al. Risk factor analysis in differentiated thyroid cancer. *Cancer* 1979;43:810-820. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/427722>.
205. Loh KC, Greenspan FS, Gee L, et al. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab* 1997;82:3553-3562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9360506>.
206. Lin JD, Kao PF, Weng HF, et al. Relative value of thallium-201 and iodine-131 scans in the detection of recurrence or distant metastasis of well differentiated thyroid carcinoma. *Eur J Nucl Med* 1998;25:695-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9662590>.
207. Brierley JD, Panzarella T, Tsang RW, et al. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. *Cancer* 1997;79:2414-2423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9191532>.
208. Castagna MG, Maino F, Cipri C, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. *Eur J Endocrinol* 2011;165:441-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21750043>.
209. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid* 2010;20:1341-1349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21034228>.
210. Vaisman F, Momesso D, Bulzico DA, et al. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. *Clin Endocrinol (Oxf)* 2012;77:132-138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22248037>.
211. Pitoia F, Bueno F, Urciuoli C, et al. Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American thyroid association and Latin American thyroid society risk of recurrence classification systems. *Thyroid* 2013;23:1401-1407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23517313>.
212. Tuttle RM. Risk-adapted management of thyroid cancer. *Endocr Pract* 2008;14:764-774. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18996800>.
213. Bilmoria KY, Zanocco K, Sturgeon C. Impact of surgical treatment on outcomes for papillary thyroid cancer. *Adv Surg* 2008;42:1-12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18953806>.
214. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 1987;102:1088-1095. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3686348>.
215. Hay ID, Grant CS, Bergstrahl EJ, et al. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery* 1998;124:958-964; discussion 964-956. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9854569>.
216. Dackiw AP, Zeiger M. Extent of surgery for differentiated thyroid cancer. *Surg Clin North Am* 2004;84:817-832. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15145237>.
217. Mazzaferri EL. Treating differentiated thyroid carcinoma: where do we draw the line? *Mayo Clin Proc* 1991;66:105-111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1988750>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

218. Massin JP, Savoie JC, Garnier H, et al. Pulmonary metastases in differentiated thyroid carcinoma. Study of 58 cases with implications for the primary tumor treatment. *Cancer* 1984;53:982-992. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6692296>.
219. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. *Laryngoscope* 2004;114:393-402. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15091208>.
220. Brito JP, Hay ID, Morris JC. Low risk papillary thyroid cancer. *BMJ* 2014;348:g3045. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24935445>.
221. Mazzaferri EL. Managing thyroid microcarcinomas. *Yonsei Med J* 2012;53:1-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22187228>.
222. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. *World J Surg* 2008;32:747-753. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18264828>.
223. Matsuzu K, Sugino K, Masudo K, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. *World J Surg* 2014;38:68-79. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24081532>.
224. Hay ID, Hutchinson ME, Gonzalez-Losada T, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery* 2008;144:980-987; discussion 987-988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19041007>.
225. Mete O, Rotstein L, Asa SL. Controversies in thyroid pathology: thyroid capsule invasion and extrathyroidal extension. *Ann Surg Oncol* 2010;17:386-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19949881>.
226. Ortiz S, Rodriguez JM, Soria T, et al. Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. *Otolaryngol Head Neck Surg* 2001;124:261-265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11240987>.
227. Grigsby PW, Reddy RM, Moley JF, Hall BL. Contralateral papillary thyroid cancer at completion thyroidectomy has no impact on recurrence or survival after radioiodine treatment. *Surgery* 2006;140:1043-1047; discussion 1047-1049. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17188155>.
228. Kim ES, Kim TY, Koh JM, et al. Completion thyroidectomy in patients with thyroid cancer who initially underwent unilateral operation. *Clin Endocrinol (Oxf)* 2004;61:145-148. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15212657>.
229. DeGroot LJ, Kaplan EL. Second operations for "completion" of thyroidectomy in treatment of differentiated thyroid cancer. *Surgery* 1991;110:936-939; discussion 939-940. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1745981>.
230. Pasieka JL, Thompson NW, McLeod MK, et al. The incidence of bilateral well-differentiated thyroid cancer found at completion thyroidectomy. *World J Surg* 1992;16:711-716; discussion 716-717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1413840>.
231. Scheumann GF, Seeliger H, Musholt TJ, et al. Completion thyroidectomy in 131 patients with differentiated thyroid carcinoma. *Eur J Surg* 1996;162:677-684. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8908447>.
232. Chao TC, Jeng LB, Lin JD, Chen MF. Completion thyroidectomy for differentiated thyroid carcinoma. *Otolaryngol Head Neck Surg* 1998;118:896-899. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9627262>.
233. Pacini F, Elisei R, Capezzzone M, et al. Contralateral papillary thyroid cancer is frequent at completion thyroidectomy with no difference in low- and high-risk patients. *Thyroid* 2001;11:877-881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11575858>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

234. Burge MR, Zeise TM, Johnsen MW, et al. Risks of complication following thyroidectomy. *J Gen Intern Med* 1998;13:24-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9462491>.
235. Dralle H, Gimm O, Simon D, et al. Prophylactic thyroidectomy in 75 children and adolescents with hereditary medullary thyroid carcinoma: German and Austrian experience. *World J Surg* 1998;22:744-750; discussion 750-741. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9606292>.
236. Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. *World J Surg* 1996;20:88-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8588420>.
237. Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. *World J Surg* 1998;22:718-724. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9606288>.
238. Hassanain M, Wexler M. Conservative management of well-differentiated thyroid cancer. *Can J Surg* 2010;53:109-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20334743>.
239. Sosa JA, Bowman HM, Tielsch JM, et al. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg* 1998;228:320-330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9742915>.
240. Robbins RJ, Schlumberger MJ. The evolving role of (131)I for the treatment of differentiated thyroid carcinoma. *J Nucl Med* 2005;46 Suppl 1:28S-37S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15653649>.
241. Leger FA, Izembart M, Dagousset F, et al. Decreased uptake of therapeutic doses of iodine-131 after 185-MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. *Eur J Nucl Med* 1998;25:242-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9580856>.
242. Muratet JP, Giraud P, Daver A, et al. Predicting the efficacy of first iodine-131 treatment in differentiated thyroid carcinoma. *J Nucl Med* 1997;38:1362-1368. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9293788>.
243. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2006;16:109-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16420177>.
244. Mazzaferri EL. Carcinoma of follicular epithelium: Radioiodine and other treatment outcomes. In: Braverman LE, Utiger RD, eds. *The Thyroid: A Fundamental and Clinical Text*. Philadelphia: Lippincott-Raven; 1996:922-945.
245. Amdur RJ, Mazzaferri EL. *Essentials of Thyroid Cancer Management*. New York: Springer Science; 2005.
246. Schlumberger MJ, Pacini F. The low utility of pretherapy scans in thyroid cancer patients. *Thyroid* 2009;19:815-816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19645614>.
247. Van Nostrand D, Aiken M, Atkins F, et al. The utility of radioiodine scans prior to iodine 131 ablation in patients with well-differentiated thyroid cancer. *Thyroid* 2009;19:849-855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19281428>.
248. Salvatori M, Perotti G, Rufini V, et al. Are there disadvantages in administering 131I ablation therapy in patients with differentiated thyroid carcinoma without a preablative diagnostic 131I whole-body scan? *Clin Endocrinol (Oxf)* 2004;61:704-710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15579184>.
249. Hay ID. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma. *J Surg Oncol* 2006;94:692-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17131429>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

250. Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin North Am* 2008;37:457-480, x. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18502337>.
251. Sisson JC, Freitas J, McDougall IR, et al. Radiation safety in the treatment of patients with thyroid diseases by radioiodine 131I : practice recommendations of the American Thyroid Association. *Thyroid* 2011;21:335-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21417738>.
252. Mazzaferri EL. Thyroid remnant 131I ablation for papillary and follicular thyroid carcinoma. *Thyroid* 1997;7:265-271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9133698>.
253. Taylor T, Specker B, Robbins J, et al. Outcome after treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma. *Ann Intern Med* 1998;129:622-627. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9786809>.
254. Ruel E, Thomas S, Dinan M, et al. Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. *J Clin Endocrinol Metab* 2015;100:1529-1536. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25642591>.
255. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* 2006;16:1229-1242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17199433>.
256. Jonklaas J, Cooper DS, Ain KB, et al. Radioiodine therapy in patients with stage I differentiated thyroid cancer. *Thyroid* 2010;20:1423-1424. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21054207>.
257. Iyer NG, Morris LG, Tuttle RM, et al. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer* 2011;117:4439-4446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21432843>.
258. Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg* 2002;26:879-885. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12016468>.
259. Hu G, Zhu W, Yang W, et al. The Effectiveness of Radioactive Iodine Remnant Ablation for Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-analysis. *World J Surg* 2016;40:100-109. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26578322>.
260. Schwartz C, Bonnetaud F, Dabakuyo S, et al. Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. *J Clin Endocrinol Metab* 2012;97:1526-1535. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22344193>.
261. Haugen BR. Radioiodine remnant ablation: current indications and dosing regimens. *Endocr Pract* 2012;18:604-610. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22849876>.
262. Castagna MG, Cevenini G, Theodoropoulou A, et al. Post-surgical thyroid ablation with low or high radioiodine activities results in similar outcomes in intermediate risk differentiated thyroid cancer patients. *Eur J Endocrinol* 2013;169:23-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23594687>.
263. Clement SC, Peeters RP, Ronckers CM, et al. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma--a systematic review. *Cancer Treat Rev* 2015;41:925-934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26421813>.
264. Brierley J, Maxon HR. Radioiodine and external radiation therapy in the treatment of thyroid cancer. In: Fagin JA, ed. *Thyroid Cancer*. Boston/Dordrecht/London: Kluwer Academic; 1998:285-317.
265. Hanscheid H, Lassmann M, Luster M, et al. Blood dosimetry from a single measurement of the whole body radioiodine retention in patients with differentiated thyroid carcinoma. *Endocr Relat Cancer* 2009;16:1283-1289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19628649>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

266. Tuttle RM, Leboeuf R, Robbins RJ, et al. Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients with thyroid cancer. *J Nucl Med* 2006;47:1587-1591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17015892>.
267. Van Nostrand D, Wartofsky L. Radioiodine in the treatment of thyroid cancer. *Endocrinol Metab Clin North Am* 2007;36:807-822, vii-viii. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17673129>.
268. Lassmann M, Reiners C, Luster M. Dosimetry and thyroid cancer: the individual dosage of radioiodine. *Endocr Relat Cancer* 2010;17:R161-172. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20448022>.
269. Hay ID, Gonzalez-Losada T, Reinalda MS, et al. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. *World J Surg* 2010;34:1192-1202. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20087589>.
270. Jarzab B, Handkiewicz-Junak D, Wloch J. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. *Endocr Relat Cancer* 2005;12:773-803. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16322322>.
271. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med* 2013;368:623-632. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23406027>.
272. Sherman SI, Tiellens ET, Sostre S, et al. Clinical utility of posttreatment radioiodine scans in the management of patients with thyroid carcinoma. *J Clin Endocrinol Metab* 1994;78:629-634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8126134>.
273. Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2003;88:3668-3673. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12915653>.
274. Pacini F, Lari R, Mazzeo S, et al. Diagnostic value of a single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. *Clin Endocrinol (Oxf)* 1985;23:405-411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4064348>.
275. Haugen BR, Pacini F, Reiners C, et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab* 1999;84:3877-3885. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10566623>.
276. Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. *J Clin Endocrinol Metab* 2005;90:5047-5057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15972576>.
277. Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997;337:888-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9302303>.
278. Mazzaferri EL, Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? *J Clin Endocrinol Metab* 2002;87:1490-1498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11932270>.
279. Castagna MG, Brilli L, Pilli T, et al. Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH-stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. *J Clin Endocrinol Metab* 2008;93:76-81. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971424>.
280. Spencer C, Petrovic I, Fatemi S, LoPresti J. Serum thyroglobulin (Tg) monitoring of patients with differentiated thyroid cancer using sensitive (second-generation) immunometric assays can be disrupted by false-negative and false-positive serum thyroglobulin autoantibody



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

misclassifications. *J Clin Endocrinol Metab* 2014;99:4589-4599. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25226290>.

281. Spencer C, LoPresti J, Fatemi S. How sensitive (second-generation) thyroglobulin measurement is changing paradigms for monitoring patients with differentiated thyroid cancer, in the absence or presence of thyroglobulin autoantibodies. *Curr Opin Endocrinol Diabetes Obes* 2014;21:394-404. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25122493>.

282. Spencer CA, Takeuchi M, Kazarosyan M. Current status and performance goals for serum thyroglobulin assays. *Clin Chem* 1996;42:164-173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8565221>.

283. Spencer CA, Lopresti JS. Measuring thyroglobulin and thyroglobulin autoantibody in patients with differentiated thyroid cancer. *Nat Clin Pract Endocrinol Metab* 2008;4:223-233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18268520>.

284. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1998;83:1121-1127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9543128>.

285. Chung JK, Park YJ, Kim TY, et al. Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. *Clin Endocrinol (Oxf)* 2002;57:215-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12153600>.

286. Chiovato L, Latrofa F, Braverman LE, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med* 2003;139:346-351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12965943>.

287. Phan HT, Jager PL, van der Wal JE, et al. The follow-up of patients with differentiated thyroid cancer and undetectable thyroglobulin (Tg) and

Tg antibodies during ablation. *Eur J Endocrinol* 2008;158:77-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18166820>.

288. Schlumberger M, Mancusi F, Baudin E, Pacini F. 131I therapy for elevated thyroglobulin levels. *Thyroid* 1997;7:273-276. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9133699>.

289. Schlumberger M, Tubiana M, De Vathaire F, et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1986;63:960-967. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3745409>.

290. Pineda JD, Lee T, Ain K, et al. Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab* 1995;80:1488-1492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7744991>.

291. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. *Thyroid* 2010;20:135-146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20151821>.

292. McGriff NJ, Csako G, Gourgiotis L, et al. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. *Ann Med* 2002;34:554-564. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12553495>.

293. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, et al. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. *J Clin Oncol* 2013;31:4046-4053. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24101052>.

294. Reverter JL, Holgado S, Alonso N, et al. Lack of deleterious effect on bone mineral density of long-term thyroxine suppressive therapy for differentiated thyroid carcinoma. *Endocr Relat Cancer* 2005;12:973-981. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16322336>.

295. Quan ML, Pasieka JL, Rorstad O. Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: a



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

systematic overview of the literature. *J Surg Oncol* 2002;79:62-69; discussion 69-70. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11754378>.

296. Pujol P, Daures JP, Nsakala N, et al. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. *J Clin Endocrinol Metab* 1996;81:4318-4323. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8954034>.

297. Cooper DS, Specker B, Ho M, et al. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. *Thyroid* 1998;8:737-744. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9777742>.

298. Burmeister LA, Goumaz MO, Mariash CN, Oppenheimer JH. Levothyroxine dose requirements for thyrotropin suppression in the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab* 1992;75:344-350. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/1639933>.

299. Salama JK, Golden DW, Yom SS, et al. ACR Appropriateness Criteria(R) thyroid carcinoma. *Oral Oncol* 2014;50:577-586. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24824115>.

300. Powell C, Newbold K, Harrington KJ, et al. External beam radiotherapy for differentiated thyroid cancer. *Clin Oncol (R Coll Radiol)* 2010;22:456-463. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20427166>.

301. Biermann M, Pixberg MK, Schuck A, et al. Multicenter study differentiated thyroid carcinoma (MSDS). Diminished acceptance of adjuvant external beam radiotherapy. *Nuklearmedizin* 2003;42:244-250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14668957>.

302. Farahati J, Reiners C, Stuschke M, et al. Differentiated thyroid cancer. Impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). *Cancer* 1996;77:172-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8630926>.

303. Simpson WJ, Panzarella T, Carruthers JS, et al. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *Int J Radiat Oncol Biol Phys* 1988;14:1063-1075. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/2454902>.

304. Chen PV, Osborne R, Ahn E, et al. Adjuvant external-beam radiotherapy in patients with high-risk well-differentiated thyroid cancer. *Ear Nose Throat J* 2009;88:E01. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19623515>.

305. Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys* 2009;74:1083-1091. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19095376>.

306. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys* 2009;73:795-801. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/18676097>.

307. Giuliani M, Brierley J. Indications for the use of external beam radiation in thyroid cancer. *Curr Opin Oncol* 2014;26:45-50. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24225415>.

308. Lee EK, Lee YJ, Jung YS, et al. Postoperative simultaneous integrated boost-intensity modulated radiation therapy for patients with locoregionally advanced papillary thyroid carcinoma: preliminary results of a phase II trial and propensity score analysis. *J Clin Endocrinol Metab* 2015;100:1009-1017. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/25581596>.

309. Expert Panel On Radiation Oncology-Bone M, Lutz ST, Lo SS, et al. ACR Appropriateness Criteria(R) non-spine bone metastases. *J Palliat Med* 2012;15:521-526. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22536988>.

310. Expert Panel on Radiation Oncology-Bone M, Lo SS, Lutz ST, et al. ACR Appropriateness Criteria (R) spinal bone metastases. *J Palliat Med*



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

2013;16:9-19. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23167547>.

311. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:45-68. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19960227>.

312. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:33-43. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19960230>.

313. Chiu AC, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. *J Clin Endocrinol Metab* 1997;82:3637-3642. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9360519>.

314. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 2006;91:2892-2899. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16684830>.

315. Droz JP, Schlumberger M, Rougier P, et al. Chemotherapy in metastatic nonanaplastic thyroid cancer: experience at the Institut Gustave-Roussy. *Tumori* 1990;76:480-483. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/2256195>.

316. Ahuja S, Ernst H. Chemotherapy of thyroid carcinoma. *J Endocrinol Invest* 1987;10:303-310. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/3624802>.

317. Sherman SI. Cytotoxic chemotherapy for differentiated thyroid carcinoma. *Clin Oncol (R Coll Radiol)* 2010;22:464-468. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20452757>.

318. Marotta V, Sciammarella C, Vitale M, et al. The evolving field of kinase inhibitors in thyroid cancer. *Crit Rev Oncol Hematol* 2015;93:60-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25240824>.

319. Cabanillas ME, Brose MS, Holland J, et al. A phase I study of cabozantinib (XL184) in patients with differentiated thyroid cancer. *Thyroid* 2014;24:1508-1514. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25102375>.

320. Schlumberger M, Brose M, Elisei R, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes Endocrinol* 2014;2:356-358. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24795243>.

321. Anderson RT, Linnehan JE, Tongbram V, et al. Clinical, safety, and economic evidence in radioactive iodine-refractory differentiated thyroid cancer: a systematic literature review. *Thyroid* 2013;23:392-407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23294230>.

322. Bales SR, Chopra IJ. Targeted treatment of differentiated and medullary thyroid cancer. *J Thyroid Res* 2011;2011:102636. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21826256>.

323. Gild ML, Bullock M, Robinson BG, Clifton-Bligh R. Multikinase inhibitors: a new option for the treatment of thyroid cancer. *Nat Rev Endocrinol* 2011;7:617-624. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21862995>.

324. Kapiteijn E, Schneider TC, Morreau H, et al. New treatment modalities in advanced thyroid cancer. *Ann Oncol* 2012;23:10-18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21471561>.

325. Perez CA, Santos ES, Arango BA, et al. Novel molecular targeted therapies for refractory thyroid cancer. *Head Neck* 2012;34:736-745. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21544895>.

326. Wang E, Karedan T, Perez CA. New insights in the treatment of radioiodine refractory differentiated thyroid carcinomas: to lenvatinib and



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

beyond. Anticancer Drugs 2015;26:689-697. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25974026>.

327. Stjepanovic N, Capdevila J. Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. Biologics 2014;8:129-139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24748771>.

328. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621-630. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25671254>.

329. Gruber JJ, Colevas AD. Differentiated thyroid cancer: focus on emerging treatments for radioactive iodine-refractory patients. Oncologist 2015;20:113-126. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25616432>.

330. Dadu R, Devine C, Hernandez M, et al. Role of salvage targeted therapy in differentiated thyroid cancer patients who failed first-line sorafenib. J Clin Endocrinol Metab 2014;99:2086-2094. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24628550>.

331. Cabanillas ME, Schlumberger M, Jarzab B, et al. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: A clinical outcomes and biomarker assessment. Cancer 2015;121:2749-2756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25913680>.

332. Tahara M, Schlumberger M, Elisei R, et al. Exploratory analysis of biomarkers associated with clinical outcomes from the study of lenvatinib in differentiated cancer of the thyroid. Eur J Cancer 2017;75:213-221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28237867>.

333. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384:319-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24768112>.

334. Schneider TC, Abdulrahman RM, Corssmit EP, et al. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial. Eur J Endocrinol 2012;167:643-650. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22918300>.

335. Massicotte MH, Brassard M, Claude-Desroches M, et al. Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: a retrospective study of the TUTHYREF network. Eur J Endocrinol 2014;170:575-582. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24424318>.

336. Brose MS, Nutting CM, Sherman SI, et al. Rationale and design of decision: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. BMC Cancer 2011;11:349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21834960>.

337. Hoftijzer H, Heemstra KA, Morreau H, et al. Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. Eur J Endocrinol 2009;161:923-931. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19773371>.

338. Cabanillas ME, Waguespack SG, Bronstein Y, et al. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab 2010;95:2588-2595. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20392874>.

339. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 2009;27:1675-1684. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19255327>.

340. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 2008;26:4714-4719. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18541894>.

341. Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res 2010;16:5260-5268. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20847059>.

342. Ravaud A, de la Fouchardiere C, Caron P, et al. A multicenter phase II study of sunitinib in patients with locally advanced or metastatic differentiated, anaplastic or medullary thyroid carcinomas: mature data from the THYSU study. Eur J Cancer 2017;76:110-117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28301826>.

343. Locati LD, Licitra L, Agate L, et al. Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. Cancer 2014;120:2694-2703. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24844950>.

344. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol 2008;26:4708-4713. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18541897>.

345. Cohen EE, Tortorici M, Kim S, et al. A Phase II trial of axitinib in patients with various histologic subtypes of advanced thyroid cancer: long-term outcomes and pharmacokinetic/pharmacodynamic analyses. Cancer Chemother Pharmacol 2014;74:1261-1270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25315258>.

346. Lim SM, Chang H, Yoon MJ, et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. Ann Oncol 2013;24:3089-3094. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24050953>.

347. Schneider TC, de Wit D, Links TP, et al. Everolimus in Patients With Advanced Follicular-Derived Thyroid Cancer: Results of a Phase II Clinical Trial. J Clin Endocrinol Metab 2017;102:698-707. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27870581>.

348. Leboulleux S, Bastholt L, Krause T, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised,

double-blind, phase 2 trial. Lancet Oncol 2012;13:897-905. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22898678>.

349. Cabanillas ME, de Souza JA, Geyer S, et al. Cabozantinib As Salvage Therapy for Patients With Tyrosine Kinase Inhibitor-Refractory Differentiated Thyroid Cancer: Results of a Multicenter Phase II International Thyroid Oncology Group Trial. J Clin Oncol 2017;35:3315-3321. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28817373>.

350. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol 2010;11:962-972. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20851682>.

351. Falchook GS, Millward M, Hong D, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. Thyroid 2015;25:71-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25285888>.

352. Rothenberg SM, McFadden DG, Palmer EL, et al. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res 2015;21:1028-1035. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25549723>.

353. Kim KB, Cabanillas ME, Lazar AJ, et al. Clinical responses to vemurafenib in patients with metastatic papillary thyroid cancer harboring BRAF(V600E) mutation. Thyroid 2013;23:1277-1283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23489023>.

354. Brose MS, Cabanillas ME, Cohen EE, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:1272-1282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27460442>.

355. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29466156>.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

356. Chou A, Fraser S, Toon CW, et al. A detailed clinicopathologic study of ALK-translocated papillary thyroid carcinoma. *Am J Surg Pathol* 2015;39:652-659. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25501013>.

357. Park G, Kim TH, Lee HO, et al. Standard immunohistochemistry efficiently screens for anaplastic lymphoma kinase rearrangements in differentiated thyroid cancer. *Endocr Relat Cancer* 2015;22:55-63. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25527510>.

358. Perot G, Soubeyran I, Ribeiro A, et al. Identification of a recurrent STRN/ALK fusion in thyroid carcinomas. *PLoS One* 2014;9:e87170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24475247>.

359. Kelly LM, Barila G, Liu P, et al. Identification of the transforming STRN-ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. *Proc Natl Acad Sci U S A* 2014;111:4233-4238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24613930>.

360. Sherman SI. Targeted therapies for thyroid tumors. *Mod Pathol* 2011;24 Suppl 2:S44-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21455200>.

361. Tuttle RM, Leboeuf R. Investigational therapies for metastatic thyroid carcinoma. *J Natl Compr Canc Netw* 2007;5:641-646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17623615>.

362. Sherman SI. Tyrosine kinase inhibitors and the thyroid. *Best Pract Res Clin Endocrinol Metab* 2009;23:713-722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19942148>.

363. Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician's perspective. *Semin Oncol* 2014;41 Suppl 2:S1-S16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24576654>.

364. Klein Hesselink EN, Steenvoorden D, Kapiteijn E, et al. Therapy of endocrine disease: response and toxicity of small-molecule tyrosine kinase inhibitors in patients with thyroid carcinoma: a systematic review and meta-analysis. *Eur J Endocrinol* 2015;172:R215-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25572389>.

365. Abdel-Rahman O, Fouad M. Risk of cardiovascular toxicities in patients with solid tumors treated with sunitinib, axitinib, cediranib or regorafenib: an updated systematic review and comparative meta-analysis. *Crit Rev Oncol Hematol* 2014;92:194-207. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25028151>.

366. Abdel-Rahman O, Fouad M. Risk of thyroid dysfunction in patients with solid tumors treated with VEGF receptor tyrosine kinase inhibitors: a critical literature review and meta analysis. *Expert Rev Anticancer Ther* 2014;14:1063-1073. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24927771>.

367. Cabanillas ME, Hu MI, Durand JB, Busaidy NL. Challenges associated with tyrosine kinase inhibitor therapy for metastatic thyroid cancer. *J Thyroid Res* 2011;2011:985780. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22007339>.

368. Krajewska J, Kukulska A, Jarzab B. Drug safety evaluation of lenvatinib for thyroid cancer. *Expert Opin Drug Saf* 2015;14:1935-1943. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26484847>.

369. Sideras K, Menefee ME, Burton JK, et al. Profound hair and skin hypopigmentation in an African American woman treated with the multi-targeted tyrosine kinase inhibitor pazopanib. *J Clin Oncol* 2010;28:e312-313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20516434>.

370. Moreno MA, Agarwal G, de Luna R, et al. Preoperative lateral neck ultrasonography as a long-term outcome predictor in papillary thyroid cancer. *Arch Otolaryngol Head Neck Surg* 2011;137:157-162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21339402>.

371. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery* 2003;134:946-954; discussion 954-945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14668727>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

372. Solorzano CC, Carneiro DM, Ramirez M, et al. Surgeon-performed ultrasound in the management of thyroid malignancy. *Am Surg* 2004;70:576-580; discussion 580-572. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15279178>.

373. Stulak JM, Grant CS, Farley DR, et al. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. *Arch Surg* 2006;141:489-494; discussion 494-486. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16702521>.

374. O'Connell K, Yen TW, Quiroz F, et al. The utility of routine preoperative cervical ultrasonography in patients undergoing thyroidectomy for differentiated thyroid cancer. *Surgery* 2013;154:697-701; discussion 701-693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24011674>.

375. Sinclair CF, Duke WS, Barbu AM, Randolph GW. Laryngeal Exam Indications and Techniques. In: Randolph GW, ed. *The Recurrent and Superior Laryngeal Nerves*. Switzerland: Springer International Publishing; 2016:17-29.

376. Carty SE, Cooper DS, Doherty GM, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid* 2009;19:1153-1158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19860578>.

377. Caron NR, Tan YY, Ogilvie JB, et al. Selective modified radical neck dissection for papillary thyroid cancer—is level I, II and V dissection always necessary? *World J Surg* 2006;30:833-840. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16555024>.

378. Stack BC, Jr., Ferris RL, Goldenberg D, et al. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. *Thyroid* 2012;22:501-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22435914>.

379. Viola D, Materazzi G, Valerio L, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical

implications derived from the first prospective randomized controlled single institution study. *J Clin Endocrinol Metab* 2015;100:1316-1324. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25590215>.

380. Haigh PI, Urbach DR, Rotstein LE. Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. *Ann Surg Oncol* 2005;12:81-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15827782>.

381. Davies L, Welch HG. Thyroid cancer survival in the United States: observational data from 1973 to 2005. *Arch Otolaryngol Head Neck Surg* 2010;136:440-444. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20479371>.

382. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg* 2007;246:375-381; discussion 381-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17717441>.

383. Kiernan CM, Parikh AA, Parks LL, Solorzano CC. Use of radioiodine after thyroid lobectomy in patients with differentiated thyroid cancer: does it change outcomes? *J Am Coll Surg* 2015;220:617-625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25667136>.

384. Brierley J, Tsang R, Panzarella T, Bana N. Prognostic factors and the effect of treatment with radioactive iodine and external beam radiation on patients with differentiated thyroid cancer seen at a single institution over 40 years. *Clin Endocrinol (Oxf)* 2005;63:418-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16181234>.

385. Chow SM, Yau S, Kwan CK, et al. Local and regional control in patients with papillary thyroid carcinoma: specific indications of external radiotherapy and radioactive iodine according to T and N categories in AJCC 6th edition. *Endocr Relat Cancer* 2006;13:1159-1172. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17158761>.

386. Lee N, Tuttle M. The role of external beam radiotherapy in the treatment of papillary thyroid cancer. *Endocr Relat Cancer* 2006;13:971-977. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17158749>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

387. Brierley JD, Tsang RW. External beam radiation therapy for thyroid cancer. *Endocrinol Metab Clin North Am* 2008;37:497-509, xi. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18502339>.
388. Pacini F, Agate L, Elisei R, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131)I whole body scan: comparison of patients treated with high (131)I activities versus untreated patients. *J Clin Endocrinol Metab* 2001;86:4092-4097. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11549631>.
389. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 2001;86:1447-1463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11297567>.
390. Burns JA, Morgenstern KE, Cahill KV, et al. Nasolacrimal obstruction secondary to I(131) therapy. *Ophthal Plast Reconstr Surg* 2004;20:126-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15083081>.
391. Haugen BR, Kane MA. Approach to the thyroid cancer patient with extracervical metastases. *J Clin Endocrinol Metab* 2010;95:987-993. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20203334>.
392. Wexler JA. Approach to the thyroid cancer patient with bone metastases. *J Clin Endocrinol Metab* 2011;96:2296-2307. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21816796>.
393. Orita Y, Sugitani I, Matsuura M, et al. Prognostic factors and the therapeutic strategy for patients with bone metastasis from differentiated thyroid carcinoma. *Surgery* 2010;147:424-431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20176243>.
394. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965-976. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21277118>.
395. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29:1125-1132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21343556>.
396. Rosen LS, Gordon D, Tchekmedyan NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer* 2004;100:2613-2621. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15197804>.
397. Vitale G, Fonderico F, Martignetti A, et al. Pamidronate improves the quality of life and induces clinical remission of bone metastases in patients with thyroid cancer. *Br J Cancer* 2001;84:1586-1590. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11401309>.
398. Eustatia-Rutten CF, Romijn JA, Guijt MJ, et al. Outcome of palliative embolization of bone metastases in differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2003;88:3184-3189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12843163>.
399. Carhill AA, Cabanillas ME, Jimenez C, et al. The noninvestigational use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. *J Clin Endocrinol Metab* 2013;98:31-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23185034>.
400. Van Nostrand D, Atkins F, Yeganeh F, et al. Dosimetrically determined doses of radioiodine for the treatment of metastatic thyroid carcinoma. *Thyroid* 2002;12:121-134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11916281>.
401. Brose MS, Worden FP, Newbold KL, et al. Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial. *J Clin Oncol* 2017;35:2692-2699. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28613956>.
402. Thomas L, Lai SY, Dong W, et al. Sorafenib in metastatic thyroid cancer: a systematic review. *Oncologist* 2014;19:251-258. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24563075>.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

403. Fallahi P, Ferrari SM, Vita R, et al. Thyroid dysfunctions induced by tyrosine kinase inhibitors. *Expert Opin Drug Saf* 2014;13:723-733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24821006>.
404. McHenry CR, Sandoval BA. Management of follicular and Hurthle cell neoplasms of the thyroid gland. *Surg Oncol Clin N Am* 1998;7:893-910. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9735140>.
405. Ustun B, Chhieng D, Van Dyke A, et al. Risk stratification in follicular neoplasm: a cytological assessment using the modified Bethesda classification. *Cancer Cytopathol* 2014;122:536-545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24753500>.
406. Phitayakorn R, McHenry CR. Follicular and Hurthle cell carcinoma of the thyroid gland. *Surg Oncol Clin N Am* 2006;15:603-623, ix-x. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16882500>.
407. Thompson LD, Wieneke JA, Paal E, et al. A clinicopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. *Cancer* 2001;91:505-524. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11169933>.
408. Hedinger CE. [Problems in the classification of thyroid tumors. Their significance for prognosis and therapy]. *Schweiz Med Wochenschr* 1993;123:1673-1681. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8211018>.
409. Goffredo P, Roman SA, Sosa JA. Hurthle cell carcinoma: a population-level analysis of 3311 patients. *Cancer* 2013;119:504-511. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22893587>.
410. Sugino K, Ito K, Mimura T, et al. Hurthle cell tumor of the thyroid: analysis of 188 cases. *World J Surg* 2001;25:1160-1163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11571953>.
411. Herrera MF, Hay ID, Wu PS, et al. Hurthle cell (oxyphilic) papillary thyroid carcinoma: a variant with more aggressive biologic behavior. *World J Surg* 1992;16:669-674; discussion 774-665. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1413835>.
412. Chindris AM, Casler JD, Bernet VJ, et al. Clinical and molecular features of Hurthle cell carcinoma of the thyroid. *J Clin Endocrinol Metab* 2015;100:55-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25259908>.
413. Wells SA, Jr., Asa SL, Dralle H, et al. Revised american thyroid association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015;25:567-610. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25810047>.
414. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009;19:565-612. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19469690>.
415. Gagel RF, Hoff AO, Cote GJ. Medullary thyroid carcinoma. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:967-988.
416. Gagel RF, Cote GJ. Pathogenesis of medullary thyroid carcinoma. In: JA F, ed. Thyroid Cancer. Boston/Dordrecht/London: Kluwer Academic; 1998:85-103.
417. Gertner ME, Kebebew E. Multiple endocrine neoplasia type 2. *Curr Treat Options Oncol* 2004;5:315-325. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15233908>.
418. Raue F, Frank-Raue K. Multiple endocrine neoplasia type 2: 2007 update. *Horm Res* 2007;68 Suppl 5:101-104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18174721>.
419. Moers AM, Landsvater RM, Schaap C, et al. Familial medullary thyroid carcinoma: not a distinct entity? Genotype-phenotype correlation in a large family. *Am J Med* 1996;101:635-641. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9003111>.
420. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

patients. Medicine (Baltimore) 1984;63:319-342. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/6503683>.

421. Vitale G, Tagliaferri P, Caraglia M, et al. Slow release lanreotide in combination with interferon-alpha2b in the treatment of symptomatic advanced medullary thyroid carcinoma. J Clin Endocrinol Metab 2000;85:983-988. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/10720027>.

422. Pacini F, Fontanelli M, Fugazzola L, et al. Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab 1994;78:826-829. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8157706>.

423. Niccoli P, Wion-Barbot N, Caron P, et al. Interest of routine measurement of serum calcitonin: study in a large series of thyroidectomized patients. The French Medullary Study Group. J Clin Endocrinol Metab 1997;82:338-341. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9024213>.

424. Ozgen AG, Hamulu F, Bayraktar F, et al. Evaluation of routine basal serum calcitonin measurement for early diagnosis of medullary thyroid carcinoma in seven hundred seventy-three patients with nodular goiter. Thyroid 1999;9:579-582. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/10411120>.

425. Horvit PK, Gagel RF. The goitrous patient with an elevated serum calcitonin--what to do? J Clin Endocrinol Metab 1997;82:335-337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9024212>.

426. Hodak SP, Burman KD. The calcitonin conundrum—is it time for routine measurement of serum calcitonin in patients with thyroid nodules? J Clin Endocrinol Metab 2004;89:511-514. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/14764754>.

427. Papi G, Corsello SM, Cioni K, et al. Value of routine measurement of serum calcitonin concentrations in patients with nodular thyroid disease: A

multicenter study. J Endocrinol Invest 2006;29:427-437. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16794366>.

428. Kouvaraki MA, Shapiro SE, Perrier ND, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005;15:531-544. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16029119>.

429. Wohllk N, Cote GJ, Bugalho MM, et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab 1996;81:3740-3745. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8855832>.

430. Elisei R, Romei C, Cosci B, et al. RET genetic screening in patients with medullary thyroid cancer and their relatives: experience with 807 individuals at one center. J Clin Endocrinol Metab 2007;92:4725-4729. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17895320>.

431. Elisei R, Alevizaki M, Conte-Devolx B, et al. 2012 European thyroid association guidelines for genetic testing and its clinical consequences in medullary thyroid cancer. Eur Thyroid J 2013;1:216-231. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24783025>.

432. Rosenthal MS, Diekema DS. Pediatric ethics guidelines for hereditary medullary thyroid cancer. Int J Pediatr Endocrinol 2011;2011:847603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21436957>.

433. Grubbs EG, Rich TA, Ng C, et al. Long-term outcomes of surgical treatment for hereditary pheochromocytoma. J Am Coll Surg 2013;216:280-289. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23317575>.

434. Kebebew E, Ituarte PH, Siperstein AE, et al. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer 2000;88:1139-1148. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/10699905>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

435. Samaan NA, Schultz PN, Hickey RC. Medullary thyroid carcinoma: prognosis of familial versus sporadic disease and the role of radiotherapy. *J Clin Endocrinol Metab* 1988;67:801-805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2901430>.
436. O'Riordain DS, O'Brien T, Weaver AL, et al. Medullary thyroid carcinoma in multiple endocrine neoplasia types 2A and 2B. *Surgery* 1994;116:1017-1023. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7985081>.
437. Lippman SM, Mendelsohn G, Trump DL, et al. The prognostic and biological significance of cellular heterogeneity in medullary thyroid carcinoma: a study of calcitonin, L-dopa decarboxylase, and histaminase. *J Clin Endocrinol Metab* 1982;54:233-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6798062>.
438. Mendelsohn G, Wells SA, Jr., Baylin SB. Relationship of tissue carcinoembryonic antigen and calcitonin to tumor virulence in medullary thyroid carcinoma. An immunohistochemical study in early, localized, and virulent disseminated stages of disease. *Cancer* 1984;54:657-662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6378353>.
439. Dottorini ME, Assi A, Sironi M, et al. Multivariate analysis of patients with medullary thyroid carcinoma. Prognostic significance and impact on treatment of clinical and pathologic variables. *Cancer* 1996;77:1556-1565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8608543>.
440. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. *Eur J Cancer* 1979;15:1033-1041. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/510341>.
441. Szinnai G, Meier C, Komminoth P, Zumsteg UW. Review of multiple endocrine neoplasia type 2A in children: therapeutic results of early thyroidectomy and prognostic value of codon analysis. *Pediatrics* 2003;111:E132-139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12563086>.
442. Romei C, Elisei R, Pinchera A, et al. Somatic mutations of the ret protooncogene in sporadic medullary thyroid carcinoma are not restricted to exon 16 and are associated with tumor recurrence. *J Clin Endocrinol Metab* 1996;81:1619-1622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8636377>.
443. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *JAMA* 1996;276:1575-1579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8918855>.
444. Wells SA, Jr., Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30:134-141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22025146>.
445. Thornton K, Kim G, Maher VE, et al. Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. *Clin Cancer Res* 2012;18:3722-3730. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22665903>.
446. Traynor K. Cabozantinib approved for advanced medullary thyroid cancer. *Am J Health Syst Pharm* 2013;70:88. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23292257>.
447. Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;31:3639-3646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24002501>.
448. Machens A, Dralle H. Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. *World J Surg* 2007;31:957-968. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17453286>.
449. Learoyd DL, Gosnell J, Elston MS, et al. Experience of prophylactic thyroidectomy in multiple endocrine neoplasia type 2A kindreds with RET codon 804 mutations. *Clin Endocrinol (Oxf)* 2005;63:636-641. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16343097>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

450. Rich TA, Feng L, Busaidy N, et al. Prevalence by age and predictors of medullary thyroid cancer in patients with lower risk germline RET proto-oncogene mutations. *Thyroid* 2014;24:1096-1106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24617864>.
451. Niederle B, Sebag F, Brauckhoff M. Timing and extent of thyroid surgery for gene carriers of hereditary C cell disease--a consensus statement of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch Surg* 2014;399:185-197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24297502>.
452. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658-5671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11739416>.
453. Machens A, Niccoli-Sire P, Hoegel J, et al. Early malignant progression of hereditary medullary thyroid cancer. *N Engl J Med* 2003;349:1517-1525. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14561794>.
454. Skinner MA, Moley JA, Dilley WG, et al. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *N Engl J Med* 2005;353:1105-1113. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16162881>.
455. Brierley J, Sherman E. The role of external beam radiation and targeted therapy in thyroid cancer. *Semin Radiat Oncol* 2012;22:254-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22687950>.
456. Brierley J, Tsang R, Simpson WJ, et al. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. *Thyroid* 1996;6:305-310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8875751>.
457. van Heerden JA, Grant CS, Gharib H, et al. Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. *Ann Surg* 1990;212:395-400; discussion 400-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2222011>.
458. Scopsi L, Sampietro G, Boracchi P, et al. Multivariate analysis of prognostic factors in sporadic medullary carcinoma of the thyroid. A retrospective study of 109 consecutive patients. *Cancer* 1996;78:2173-2183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8918412>.
459. Tisell LE, Hansson G, Jansson S, Salander H. Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. *Surgery* 1986;99:60-66. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3942001>.
460. Moley JF, Debenedetti MK, Dilley WG, et al. Surgical management of patients with persistent or recurrent medullary thyroid cancer. *J Intern Med* 1998;243:521-526. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9681853>.
461. Fleming JB, Lee JE, Bouvet M, et al. Surgical strategy for the treatment of medullary thyroid carcinoma. *Ann Surg* 1999;230:697-707. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561095>.
462. Haddad RI. How to incorporate new tyrosine kinase inhibitors in the treatment of patients with medullary thyroid cancer. *J Clin Oncol* 2013;31:3618-3620. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24002516>.
463. Aleman JO, Farooki A, Girotra M. Effects of tyrosine kinase inhibition on bone metabolism: untargeted consequences of targeted therapies. *Endocr Relat Cancer* 2014;21:R247-259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24478055>.
464. Sherman SI. Lessons learned and questions unanswered from use of multitargeted kinase inhibitors in medullary thyroid cancer. *Oral Oncol* 2013;49:707-710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23582411>.
465. Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol* 2011;29:2660-2666. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21606412>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

466. Robinson BG, Paz-Ares L, Krebs A, et al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Endocrinol Metab* 2010;95:2664-2671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20371662>.
467. Grande E, Kreissl MC, Filetti S, et al. Vandetanib in advanced medullary thyroid cancer: review of adverse event management strategies. *Adv Ther* 2013;30:945-966. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24249433>.
468. Schlumberger M, Elisei R, Muller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. *Ann Oncol* 2017;28:2813-2819. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29045520>.
469. Sherman SI, Clary DO, Elisei R, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. *Cancer* 2016;122:3856-3864. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27525386>.
470. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19097774>.
471. Wells SA, Jr., Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol* 2010;28:767-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20065189>.
472. Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. *J Clin Endocrinol Metab* 2009;94:1493-1499. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19258410>.
473. Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *J Clin Oncol* 2010;28:2323-2330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20368568>.
474. Kelleher FC, McDermott R. Response to sunitinib in medullary thyroid cancer. *Ann Intern Med* 2008;148:567. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18378960>.
475. Bible KC, Suman VJ, Molina JR, et al. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. *J Clin Endocrinol Metab* 2014;99:1687-1693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24606083>.
476. Schlumberger M, Jarzab B, Cabanillas ME, et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. *Clin Cancer Res* 2016;22:44-53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26311725>.
477. Orlandi F, Caraci P, Berruti A, et al. Chemotherapy with dacarbazine and 5-fluorouracil in advanced medullary thyroid cancer. *Ann Oncol* 1994;5:763-765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7826911>.
478. Nocera M, Baudin E, Pellegriti G, et al. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. *Groupe d'Etude des Tumeurs a Calcitonine (GETC)*. *Br J Cancer* 2000;83:715-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10952773>.
479. Schlumberger M, Abdelmoumene N, Delisle MJ, Couette JE. Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. *The Groupe d'Etude des Tumeurs a Calcitonine (GETC)*. *Br J Cancer* 1995;71:363-365. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7530987>.
480. Gulati AP, Krantz B, Moss RA, et al. Treatment of multiple endocrine neoplasia 1/2 tumors: case report and review of the literature. *Oncology* 2013;84:127-134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23235517>.
481. Santarpia L, Ye L, Gagel RF. Beyond RET: potential therapeutic approaches for advanced and metastatic medullary thyroid carcinoma. *J*



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

Intern Med 2009;266:99-113. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19522829>.

482. Cakir M, Grossman AB. Medullary thyroid cancer: molecular biology and novel molecular therapies. Neuroendocrinology 2009;90:323-348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19468197>.

483. Cerrato A, De Falco V, Santoro M. Molecular genetics of medullary thyroid carcinoma: the quest for novel therapeutic targets. J Mol Endocrinol 2009;43:143-155. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19383830>.

484. Chatal JF, Campion L, Kraeber-Bodere F, et al. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group. J Clin Oncol 2006;24:1705-1711. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16549819>.

485. Salaun PY, Campion L, Bournaud C, et al. Phase II trial of anticarcinoembryonic antigen pretargeted radioimmunotherapy in progressive metastatic medullary thyroid carcinoma: biomarker response and survival improvement. J Nucl Med 2012;53:1185-1192. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22743249>.

486. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. Ann Surg Oncol 2006;13:453-464. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16474910>.

487. Kebebew E, Greenspan FS, Clark OH, et al. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer 2005;103:1330-1335. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15739211>.

488. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-1139. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23130564>.

489. Moretti F, Farsetti A, Soddu S, et al. p53 re-expression inhibits proliferation and restores differentiation of human thyroid anaplastic carcinoma cells. Oncogene 1997;14:729-740. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9038381>.

490. Maatouk J, Barklow TA, Zakaria W, Al-Abbad MA. Anaplastic thyroid carcinoma arising in long-standing multinodular goiter following radioactive iodine therapy: report of a case diagnosed by fine needle aspiration. Acta Cytol 2009;53:581-583. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19798888>.

491. Aldinger KA, Samaan NA, Ibanez M, Hill CS, Jr. Anaplastic carcinoma of the thyroid: a review of 84 cases of spindle and giant cell carcinoma of the thyroid. Cancer 1978;41:2267-2275. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/657091>.

492. Keutgen XM, Sadowski SM, Kebebew E. Management of anaplastic thyroid cancer. Gland Surg 2015;4:44-51. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/25713779>.

493. Sherman SI. Anaplastic carcinoma: Clinical aspects. In: Wartofsky L, Van Nostrand D, eds. Thyroid Cancer: A Comprehensive Guide to Clinical Management, 2nd ed. Totowa, NJ: Humana Press; 2006:629-632.

494. Takashima S, Morimoto S, Ikezoe J, et al. CT evaluation of anaplastic thyroid carcinoma. AJR Am J Roentgenol 1990;154:1079-1085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2108546>.

495. Neff RL, Farrar WB, Kloos RT, Burman KD. Anaplastic thyroid cancer. Endocrinol Metab Clin North Am 2008;37:525-538, xi. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/18502341>.

496. Wein RO, Weber RS. Anaplastic thyroid carcinoma: palliation or treatment? Curr Opin Otolaryngol Head Neck Surg 2011;19:113-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21252667>.

497. Untch BR, Olson JA, Jr. Anaplastic thyroid carcinoma, thyroid lymphoma, and metastasis to thyroid. Surg Oncol Clin N Am 2006;15:661-679, x. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16882503>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

498. Shaha AR. Airway management in anaplastic thyroid carcinoma. *Laryngoscope* 2008;118:1195-1198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18438260>.
499. Venkatesh YS, Ordonez NG, Schultz PN, et al. Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. *Cancer* 1990;66:321-330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1695118>.
500. Sugitani I, Miyauchi A, Sugino K, et al. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. *World J Surg* 2012;36:1247-1254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22311136>.
501. Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid* 2011;21:1183-1189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21936674>.
502. Mani N, McNamara K, Lowe N, et al. Management of the compromised airway and role of tracheotomy in anaplastic thyroid carcinoma. *Head Neck* 2016;38:85-88. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25215461>.
503. Junor EJ, Paul J, Reed NS. Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy. *Eur J Surg Oncol* 1992;18:83-88. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1582515>.
504. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery* 2001;130:1028-1034. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11742333>.
505. Stavas MJ, Shinohara ET, Attia A, et al. Short course high dose radiotherapy in the treatment of anaplastic thyroid carcinoma. *J Thyroid Res* 2014;2014:764281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25379320>.
506. Dumke AK, Pelz T, Vordermark D. Long-term results of radiotherapy in anaplastic thyroid cancer. *Radiat Oncol* 2014;9:90. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24685141>.
507. Burnison CM, Lim S. Multimodal approach to anaplastic thyroid cancer. *Oncology (Williston Park)* 2012;26:378-384, 390-378. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22655531>.
508. Wang Y, Tsang R, Asa S, et al. Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer* 2006;107:1786-1792. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16967442>.
509. Nachalon Y, Stern-Shavit S, Bachar G, et al. Aggressive Palliation and Survival in Anaplastic Thyroid Carcinoma. *JAMA Otolaryngol Head Neck Surg* 2015;141:1128-1132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26512447>.
510. De Crevoisier R, Baudin E, Bachet A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;60:1137-1143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15519785>.
511. Kim JH, Leeper RD. Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy. *Cancer* 1987;60:2372-2375. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3664425>.
512. Mohebati A, Dilorenzo M, Palmer F, et al. Anaplastic thyroid carcinoma: a 25-year single-institution experience. *Ann Surg Oncol* 2014;21:1665-1670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24554064>.
513. Derbel O, Limem S, Segura-Ferlay C, et al. Results of combined treatment of anaplastic thyroid carcinoma (ATC). *BMC Cancer* 2011;11:469. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22044775>.



# NCCN Guidelines Version 2.2020

## Thyroid Carcinoma

514. Wallin G, Lundell G, Tennvall J. Anaplastic giant cell thyroid carcinoma. *Scand J Surg* 2004;93:272-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15658667>.
515. Smallridge RC. Approach to the patient with anaplastic thyroid carcinoma. *J Clin Endocrinol Metab* 2012;97:2566-2572. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22869844>.
516. Bhatia A, Rao A, Ang KK, et al. Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. *Head Neck* 2010;32:829-836. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19885924>.
517. Sun XS, Sun SR, Guevara N, et al. Chemoradiation in anaplastic thyroid carcinomas. *Crit Rev Oncol Hematol* 2013;86:290-301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23218594>.
518. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). *Cancer Radiother* 2011;15:555-559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21802333>.
519. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): Contents. *J ICRU* 2010;10:NP. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24173332>.
520. Sosa JA, Balkissoon J, Lu SP, et al. Thyroidectomy followed by fosbretabulin (CA4P) combination regimen appears to suggest improvement in patient survival in anaplastic thyroid cancer. *Surgery* 2012;152:1078-1087. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23158178>.
521. Swaak-Kragten AT, de Wilt JH, Schmitz PI, et al. Multimodality treatment for anaplastic thyroid carcinoma--treatment outcome in 75 patients. *Radiother Oncol* 2009;92:100-104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19328572>.
522. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. *J Clin Oncol* 2018;36:7-13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29072975>.
523. Higashiyama T, Ito Y, Hirokawa M, et al. Induction chemotherapy with weekly paclitaxel administration for anaplastic thyroid carcinoma. *Thyroid* 2010;20:7-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20025538>.
524. Ain KB. Anaplastic thyroid carcinoma: behavior, biology, and therapeutic approaches. *Thyroid* 1998;8:715-726. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9737368>.
525. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. *Thyroid* 2000;10:587-594. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10958311>.
526. U.S. Food and Drug Administration. FDA approves dabrafenib plus trametinib for anaplastic thyroid cancer with BRAF V600E mutation. 2018. Available at: <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606708.htm>. Accessed August 24, 2018.
527. Brose MS, Albert CM, Wagenseck SG, et al. Activity of larotrectinib in patients with advanced TRK fusion thyroid cancer [abstract]. 88th Annual Meeting of the American Thyroid Association 2018;Clinical Oral Presentation 10. Available at: <https://www.liebertpub.com/doi/pdf/10.1089/thy.2018.29065.abstracts>.
528. U.S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018. Available at: <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626720.htm>. Accessed November 30, 2018.
529. Smallridge RC, Marlow LA, Copland JA. Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. *Endocr Relat Cancer* 2009;16:17-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18987168>.



## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

530. Savvides P, Nagaiah G, Lavertu P, et al. Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. *Thyroid* 2013;23:600-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23113752>.
531. Perri F, Lorenzo GD, Scarpati GD, Buonerba C. Anaplastic thyroid carcinoma: A comprehensive review of current and future therapeutic options. *World J Clin Oncol* 2011;2:150-157. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21611089>.
532. Deshpande HA, Gettinger SN, Sosa JA. Novel chemotherapy options for advanced thyroid tumors: small molecules offer great hope. *Curr Opin Oncol* 2008;20:19-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18043252>.
533. Mooney CJ, Nagaiah G, Fu P, et al. A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome. *Thyroid* 2009;19:233-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19265494>.
534. Ha HT, Lee JS, Urba S, et al. A phase II study of imatinib in patients with advanced anaplastic thyroid cancer. *Thyroid* 2010;20:975-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20718683>.
535. Bible KC, Suman VJ, Menefee ME, et al. A multiinstitutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. *J Clin Endocrinol Metab* 2012;97:3179-3184. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22774206>.
536. Antonelli A, Fallahi P, Ulisse S, et al. New targeted therapies for anaplastic thyroid cancer. *Anticancer Agents Med Chem* 2012;12:87-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22043992>.
537. Sosa JA, Elisei R, Jarzab B, et al. Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. *Thyroid* 2014;24:232-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23721245>.
538. Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid* 2011;21:25-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21162687>.
539. Nagaiah G, Hossain A, Mooney CJ, et al. Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment. *J Oncol* 2011;2011:542358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21772843>.
540. Siironen P, Hagstrom J, Maenpaa HO, et al. Anaplastic and poorly differentiated thyroid carcinoma: therapeutic strategies and treatment outcome of 52 consecutive patients. *Oncology* 2010;79:400-408. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21455012>.
541. Brignardello E, Gallo M, Baldi I, et al. Anaplastic thyroid carcinoma: clinical outcome of 30 consecutive patients referred to a single institution in the past 5 years. *Eur J Endocrinol* 2007;156:425-430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17389456>.
542. Yau T, Lo CY, Epstein RJ, et al. Treatment outcomes in anaplastic thyroid carcinoma: survival improvement in young patients with localized disease treated by combination of surgery and radiotherapy. *Ann Surg Oncol* 2008;15:2500-2505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18581185>.
543. Park JW, Choi SH, Yoon HI, et al. Treatment outcomes of radiotherapy for anaplastic thyroid cancer. *Radiat Oncol J* 2018;36:103-113. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29983030>.
544. Rao SN, Zaferes M, Dadu R, et al. Patterns of Treatment Failure in Anaplastic Thyroid Carcinoma. *Thyroid* 2017;27:672-681. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28068873>.
545. Heron DE, Karimpour S, Grigsby PW. Anaplastic thyroid carcinoma: comparison of conventional radiotherapy and hyperfractionation chemoradiotherapy in two groups. *Am J Clin Oncol* 2002;25:442-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12393980>.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 2.2020 Thyroid Carcinoma

546. Kunstman JW, Juhlin CC, Goh G, et al. Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing. *Hum Mol Genet* 2015;24:2318-2329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25576899>.

547. Rosove MH, Peddi PF, Glaspy JA. BRAF V600E inhibition in anaplastic thyroid cancer. *N Engl J Med* 2013;368:684-685. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23406047>.

548. Takano T, Ito Y, Hirokawa M, et al. BRAF V600E mutation in anaplastic thyroid carcinomas and their accompanying differentiated carcinomas. *Br J Cancer* 2007;96:1549-1553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17453004>.



A large, semi-transparent circular graphic is centered on the page. Inside the circle, the words "Discussion", "update in", and "progress" are stacked vertically in a large, bold, sans-serif font. The text is light gray, and the entire graphic is contained within two concentric circles.

Discussion  
update in  
progress