National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thyroid Carcinoma

Version 2.2017 — May 17, 2017

NCCN.org

Continue

NCCN Guidelines Version 2.2017 Panel Members
Thyroid Carcinoma

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

William M. Lydiatt, MD/Vice-Chair ¶ ζ
Fred & Pamela Buffett Cancer Center

Lindsay Bischoff. MD ð
Vanderbilt-Ingram Cancer Center

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

David Byrd, MD ¶
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Glenda Callender, MD ¶
Yale Cancer Center/Smilow Cancer Hospital

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

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

Hormoz Ehya, MD ≠
Fox Chase Cancer Center

Megan Haymart, MD Þ ð
University of Michigan Comprehensive Cancer Center

NCCN
Lisa A. Gurski, PhD
Karin G. Hoffmann, RN, CCM
Miranda Hughes, PhD

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 ð
City of Hope Comprehensive Cancer Center

Peter Kopp, MD ð Þ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Dominick M. Lamonica, MD Þ Φ
Roswell Park Cancer Institute

Bryan McIver, MD, PhD ð
Moffitt Cancer Center

Jeffrey F. Moley, MD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Christian Nasr, MD ð
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

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

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

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

Randall P. Scheri, MD ¶
Duke Cancer Institute

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

Rebecca Sippel, MD ¶
University of Wisconsin Carbone Cancer Center

Robert C. Smallridge, MD ð
Mayo Clinic Cancer Center

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

Thomas N. Wang, MD, PhD ¶
University of Alabama at Birmingham Comprehensive Cancer Center

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

ð Endocrinology
¶ Surgery/Surgical oncology
† Medical oncology
≠ Pathology
Þ Internal medicine
Φ Nuclear medicine
ζ Otolaryngology
*Writing Committee Member

Continue

NCCN Guidelines Panel Disclosures

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/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

General
- For imaging, the target anatomy and the use of contrast was added to CT and whole-body was added to PET/CT as appropriate throughout the guidelines.
- For lenvatinib "preferred" was added as appropriate throughout the guidelines.

Thyroid Carcinoma

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

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

Thyroid Carcinoma continued

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

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

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

Papillary Carcinoma

PAP-1

- Diagnostic Procedures
  - 3rd bullet was revised: "Consider evaluation of vocal cord mobility *(ultrasound, mirror indirect laryngoscopy, or fiberoptic laryngoscopy)"* (Also for FOLL-1, HÜRT-1, MEDU-1, and ANAP-1)
  - 4th bullet was revised: *"Consider FNA for* suspicious *lateral neck* nodes ~~in lateral neck should be further evaluated by ultrasound-guided FNA for staging and guiding extent of surgery~~"
  - A footnote was added: *"Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck."* (Also for FOLL-1, HÜRT-1, MEDU-1, and ANAP-1)
- Preoperative or Intraoperative Decision-Making Criteria
  - 5th bullet under, "Indications for total thyroidectomy or lobectomy, if all criteria present" was revised: "Tumor ~~<~~≤4 cm in diameter"
- Primary Treatment
  - 1st statement was revised: "Total thyroidectomy Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease ~~Consider prophylactic central neck dissection (level VI) (category 2B)~~
  - Lobectomy + isthmusectomy (category 2B)
    - ◊ 3rd bullet was added under "All of the following": *"NIFTP pathologic diagnosis"* (Also for FOLL-1 and HÜRT-1)
    - ◊ A footnote was added: *"RAI not recommended after lobectomy."* (Also for FOLL-1 and HÜRT-1)
    - ◊ A footnote was added: *"Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), has been reclassified and only lobectomy is needed."* (Also for PAP-2, FOLL-1 and HÜRT-1)
- Footnote "b" was revised: *"*Use of iodinated contrast ~~will delay treatment with RAI but is required~~ is required for optimal cervical imaging using CT, *although* iodinated contrast will delay treatment with RAI*."* (Also for FOLL-1 and HÜRT-1)

Papillary Carcinoma continued

PAP-1

- Footnote "d" was revised: *"*Completion thyroidectomy is not required for small volume pathologic N1*A* ~~micro~~metastases (~~≤~~<5 involved nodes with no ~~micro~~metastasis, >*2 mm* ~~0.5 cm~~ in largest dimension). See (PAP-4)." (Also for PAP-2)
- A footnote was removed: "Possible benefit to reduce recurrence for patients with T3-T4 lateral disease must be balanced with risk of hypoparathyroidism and recurrent laryngeal nerve damage."

PAP-4

- "RAI not typically recommended (if all present)"
  - 2nd bullet was revised; "<~~1~~ *2* cm" (Also for HÜRT-3)
- "RAI selectively recommended (if any present)"
  - 1st bullet was revised: "Primary tumor ~~1~~ *2*–4 cm" (Also for HÜRT-3)

PAP-5

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

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

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Updates Thyroid Carcinoma

Papillary Carcinoma continued

PAP-7

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

PAP-8

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

PAP-9

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

PAP-10

- A bullet was removed: "Active surveillance may be appropriate in asymptomatic patients with indolent disease. (See PAP-8)" (Also for FOLL-10 and HURT-10)

Follicular Carcinoma

FOLL-9

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

FOLL-10

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

Medullary Carcinoma

MEDU-1

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

MEDU-2

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

MEDU-3

- Primary Treatment
  - 4th bullet was revised: "~~Consider~~ Adjuvant EBRT/IMRT ~~for gross residual disease~~ *is* rarely recommended" (Also for MEDU-4)

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

Medullary Carcinoma continued

MEDU-5

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

MEDU-6

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

MEDU-7

- **Symptomatic disease or progression**
  - **2nd bullet was revised: "EBRT/IMRT for ~~focal~~ *local* symptoms (Also for ANAP-2)**
  - **Footnote "t" was revised: "While not FDA approved for treatment of medullary thyroid cancer, other commercially available small-molecule kinase inhibitors (such as sorafenib, sunitinib, *lenvatinib*, or pazopanib) can be considered if clinical trials, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib"**

Anaplastic Carcinoma

ANAP-1

- **Diagnostic Procedures**
  - **7th bullet was revised: "~~18~~ FDG PET/CT *(skull base to mid-thigh)*" (Also for ANAP-2)**
  - **9th bullet was added: *"Direct exam of larynx"***

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

CLINICAL PRESENTATION | **WORKUP**

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

→ **Thyroid nodule(s) with low TSH** → **Radioiodine imaging thyroid uptake and scan**
  - → **Autonomously functioning (hot)** → **Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)[b]**
  - → **Hypofunctional** → **Consider fine-needle aspiration (FNA) or ultrasound-guided FNA based on clinical and sonographic features** → **See Sonographic Features[b] (THYR-2)**

→ **Thyroid nodule(s) with normal or elevated TSH[a]** → **Consider fine-needle aspiration (FNA) or ultrasound-guided FNA based on clinical and sonographic features** → **See Sonographic Features[b] (THYR-2)**

[a]Evaluate and treat for hypothyroidism as clinically indicated.
[b]For nodules not meeting criteria for FNA, or nodules that appear to be benign by ultrasound or FNA, surveillance should include repeat ultrasound after 6–12 months; if stable for 1–2 years, then subsequent ultrasound can be considered at 3- to 5-year intervals.

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

SONOGRAPHIC FEATURES

	Threshold for FNA
Solid nodule	
• With suspicious sonographic features[c]	≥1.0 cm
• Without suspicious sonographic features	≥1.5 cm
Mixed cystic-solid nodule	
• With suspicious sonographic features[c]	Solid component >1 cm
• Without suspicious sonographic features	Solid component >1.5 cm
Spongiform nodule[d]	≥2.0 cm
Simple cyst	Not indicated[e]
Suspicious cervical lymph node[f,g]	FNA node ± FNA-associated thyroid nodule(s)

→ **FNA, if indicated** **(See THYR-3 and THYR-4)** **or Observe[b]**

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

[b]For nodules not meeting criteria for FNA, or nodules that appear to be benign by ultrasound or FNA, surveillance should include repeat ultrasound after 6–12 months; if stable for 1–2 years, then subsequent ultrasound can be considered at 3- to 5-year intervals.
[c]Suspicious sonographic features include hypoechoic, microcalcifications, infiltrative margins, and taller than wide in the transverse plane. Sonographic features associated with a low risk of malignancy include spongiform nodules, isoechoic or hyperechoic solid nodules, and mixed solid-cystic nodules without any of the suspicious features listed above.
[d]Aggregation of multiple microcystic components in more than 50% of the volume of the nodule.
[e]Except as therapeutic modality.
[f]Tg washout may be helpful in diagnosis of lymph node metastases.
[g]Suspicious lymph node features may include hypoechoic, rounded, absence of fatty hilum, cystic or partially cystic, and/or microcalcifications.

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

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification (Cibas ES et al. Am J Clin Pathol 2009;132:658-665). Cytology reports should be interpreted in light of terminology used by local cytopathologists.

FNA RESULTS			TREATMENT	
Carcinoma or suspicious for carcinoma	Papillary or suspicious for papillary		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[h,i]	High clinical and/or radiographic suspicion of malignancy[k]	Yes	Consider lobectomy or total thyroidectomy[l] for definitive diagnosis/treatment	See PAP-1 See FOLL-1 See HÜRT-1
		No	• Consider diagnostic lobectomy • Consider molecular diagnostics for follicular cell neoplasm[i,m] • Consider observation if low risk or patient preference	See THYR-4
Atypia of undetermined significance/ Follicular lesion of undetermined significance[i,j] (AUS/FLUS)	High clinical and/or radiographic suspicion of malignancy[k]	Yes	Consider lobectomy or total thyroidectomy[l] for definitive diagnosis/treatment	See PAP-1 See FOLL-1 See HÜRT-1
		No	• Consider diagnostic lobectomy • Consider molecular diagnostics[i] • Repeat FNA[n] • Observe	See THYR-4

[h]Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 20%–30%.
[i]The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (FLUS)) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see (PAP-1). If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.
[j]Alternative terms include: rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%–10%.
[k]Based on rapid growth of nodule, imaging, physical exam, age, clinical history of radiation, and family history.
[l]Total thyroidectomy may be considered for Hürthle cell, history of radiation exposure, or contralateral lobe lesions.
[m]Molecular diagnostics are not recommended for Hürthle cell neoplasm.
[n]Consider second opinion pathology.

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

FNA RESULTS → **TREATMENT**

AUS/FLUS[i,j] → **Consider molecular diagnostics[i]**
- **Molecular diagnostics**
  - **Not done**
  - **Not informative**

  → **Observe or Consider lobectomy for definitive diagnosis/treatment[o]**
- **Molecular diagnostics indicate benign lesion[i]** → **Observe or Consider lobectomy for definitive diagnosis/treatment[o]**
- **Molecular diagnostics suggestive of malignancy** → **Consider lobectomy or total thyroidectomy for definitive diagnosis/treatment**

Follicular neoplasm[h,i] → **Consider molecular diagnostics[i,m]**
- **Molecular diagnostics suggestive of malignancy** → **Consider lobectomy or total thyroidectomy for definitive diagnosis/treatment**
- **Molecular diagnostics**
  - **Not done**
  - **Not informative**

  → **Consider lobectomy or total thyroidectomy for definitive diagnosis/treatment**
- **Molecular diagnostics indicate benign lesion[i]** → **Observe or consider lobectomy for definitive diagnosis/treatment[i,o]**

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification (Cibas ES et al. Am J Clin Pathol 2009; 132:658-665). Cytology reports should be interpreted in light of terminology used by local cytopathologists.

[h] Alternative term: Suspicious for follicular neoplasm. Estimated risk of malignancy is 20%–30%.

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

[j] Alternative terms include: rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%–10%.

[m] Molecular diagnostics are not recommended for Hürthle cell neoplasm.

[o] Clinical risk factors, sonographic patterns, and patient preference can help determine whether observation or lobectomy is appropriate.

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

FNA RESULTS		TREATMENT
Thyroid lymphoma	→	**See NCCN Guidelines for B-cell Lymphomas**
Insufficient biopsy, nondiagnostic	**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**
Benign[p]	→	**• Observe[q]** **• If nodule growth[r], repeat FNA or consider surgery**

[p]Includes nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, and Hashimoto's thyroiditis. Estimated risk of malignancy is approximately 5% or less; consider observation.

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

[r]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.

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification (Cibas ES et al. Am J Clin Pathol 2009; 132:658-665). 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 cancer patient 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.
- Given the potential toxicities associated with TSH-suppressive doses of levothyroxine—including cardiac tachyarrhythmias (especially in the elderly) and bone demineralization (particularly in post-menopausal women) as well as frank symptoms of thyrotoxicosis—the risk and benefit of TSH-suppressive therapy must be balanced for each individual patient.
- Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d).

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

PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA

- Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic medullary thyroid cancer (MTC) and in radio iodine-refractory differentiated thyroid cancer (DTC).[1,2,3]
- When considering kinase inhibitor therapy for individual patients, several factors should be considered.
  - Kinase inhibitor therapy can be associated with progression-free survival, but is not curative.
  - Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.
  - The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.
- The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have drug-induced side effects.
- Optimal management of kinase inhibitor side effects is essential. Where available, guidelines outlining the management of the dermatologic, hypertensive, and gastrointestinal side effects of kinase inhibitors can be used; side effects have been fatal.[4,5,6,7] In addition, dose modification may be required, including dose holds and dose reductions.

[1]Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134-141.
[2]Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. Lancet 2014;384(9940):319-328.
[3]Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639-3646.
[4]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.
[5]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.
[6]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.
[7]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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Papillary carcinoma[a] →

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

→ **Indications for total thyroidectomy (any present):**
- Known distant metastases
- Extrathyroidal extension
- Tumor >4 cm in diameter
- Cervical lymph node metastases[d]
- Poorly differentiated
- Consider for prior radiation exposure (category 2B)
- Consider bilateral nodularity

→ Total thyroidectomy
Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease
→ See Postsurgical Evaluation (PAP-3)

→ **Indications for total thyroidectomy or lobectomy, if all criteria present:**
- No prior radiation exposure
- No distant metastases
- No cervical lymph node metastases
- No extrathyroidal extension
- Tumor ≤4 cm in diameter

→ Total thyroidectomy (category 2B) → See Postsurgical Evaluation (PAP-3)

or

Lobectomy + isthmusectomy (category 2B)[e]

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

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

→ **All of the following:**
- Negative margins
- No contralateral lesion
- NIFTP pathologic diagnosis[f]

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

→ See Surveillance and Maintenance (PAP-7)

[a]There is a potential role for lobectomy with or without frozen section if FNA is suspicious but not diagnostic for papillary carcinoma.
[b]Use of iodinated contrast is required for optimal cervical imaging using CT, although iodinated contrast will delay treatment with RAI.
[c]Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[d]Completion thyroidectomy is not required for small volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm in largest dimension). See (PAP-4).
[e]RAI not recommended after lobectomy.
[f]Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), has been reclassified and only lobectomy is needed.
[g]Useful for future follow-up and assessing trend patterns.
[h]See Principles of TSH Suppression (THYR-A).

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

CLINICAL PRESENTATION

PRIMARY TREATMENT

Papillary carcinoma found post-lobectomy →

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

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

→ **Completion of thyroidectomy**
- Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease
- Consider prophylactic central neck dissection (level VI) (category 2B)[i]

→ See Postsurgical Evaluation (PAP-3)

→ **Tumor 1–4 cm in diameter or Lymphatic invasion**

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

or

Observe[j] (category 2B) → **Consider levothyroxine therapy to keep TSH low or normal[h]** → See Surveillance and Maintenance (PAP-7)

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

→ **Observe[j]** → **Consider levothyroxine therapy to keep TSH low or normal[h]** → See Surveillance and Maintenance (PAP-7)

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

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

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

[j]Measurement of thyroglobulin and antithyroglobulin antibodies is useful for future follow-up and assessing trend patterns.

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

POSTSURGICAL EVALUATION

- **No gross residual disease in neck** → See Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (PAP-4)
- **Gross residual disease in neck**
  - **Resectable** → **Resect, if possible**
    - **No gross residual disease** → See Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (PAP-4)
    - **Gross residual disease** → see below
  - **Unresectable** →
    - **TSH + Tg measurement + antithyroglobulin antibodies (6–12 wk postoperatively)**
    - **Total body radioiodine imaging (category 2B)**
      - **Suspected or proven inadequate RAI uptake** → **Observe or Consider External-beam radiation therapy (EBRT/IMRT) if disease is threatening vital structures**
      - **Adequate RAI uptake** →
      - **No RAI imaging performed** →
        - **Radioiodine treatment (preferred)**
        - **Post-treatment ^{131}I whole body imaging**
        - **Consider EBRT/IMRT**
          → **Suppress TSH with levothyroxine**[h] → See Surveillance and Maintenance (PAP-7)

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

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

CLINICOPATHOLOGIC FACTORS	CONSIDERATION FOR INITIAL POSTOPERATIVE RAI THERAPY AFTER TOTAL THYROIDECTOMY	
RAI not typically recommended (if all present): • Classic papillary thyroid carcinoma (PTC) • Primary tumor <2 cm • Intrathyroidal • Unifocal or multifocal • No detectable anti-Tg antibodies • Postoperative unstimulated Tg <1 ng/mL[k]	→	RAI not typically indicated, See (PAP-7)
RAI selectively recommended (if any present): • Primary tumor 2–4 cm • High-risk histology[l] • Lymphatic invasion • Cervical lymph node metastases • Macroscopic multifocality (one focus >1 cm • Postoperative unstimulated Tg <5–10 ng/mL[k]	RAI ablation is not required in patients with classic PTC who have T1b/T2 (1–4 cm) cN0 disease or small-volume N1a disease (fewer than 3–5 metastatic lymph nodes with 2–5 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 not typically indicated, See (PAP-7)
	RAI ablation is recommended when the combination of individual clinical factors (such as the size of the primary tumor, histology, degree of lymphatic invasion, lymph node metastases, postoperative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.	→ RAI being considered, See (PAP-5)
RAI typically recommended (if any present): • Gross extrathyroidal extension • Primary tumor >4 cm • Postoperative unstimulated Tg >5–10 ng/mL[k,m]	→	RAI being considered, See (PAP-5)
Known or suspected distant metastases at presentation	→	Amenable to RAI See (PAP-6)
Gross residual disease not amenable to RAI therapy	→	See (PAP-9)

[k]Tg values obtained 6–12 weeks after total thyroidectomy.
[l]ie, poorly differentiated, tall cell, columnar cell, and hobnail variants.
[m]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 therapy, See (Discussion)

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

RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → **Clinicopathologic findings prompting consideration for RAI, without gross residual disease or known distant metastasis** See (PAP-4) → **Consider pretreatment ^{123}I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH); (category 2B)[n,o]**

- **No or minor thyroid bed uptake on scan, unstimulated Tg <1 ng/mL (with negative anti-Tg antibodies)** → **Follow without RAI ablation**
- **Suspected[o,p] or proven thyroid bed uptake** → **Follow without RAI ablation or Selective use of RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)[q,r]; post-treatment imaging (whole body RAI scan)**
- **Suspected[o,p] or proven radioiodine avid metastatic foci** → **RAI therapy (100–200 mCi)[q,r]; post-treatment imaging (whole body RAI scan)**

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

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

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

[p]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

[q]The administered activity of RAI therapy should be adjusted for pediatric patients.

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

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

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

6–12 weeks post-thyroidectomy → **Known or suspected distant metastases at presentation** See (PAP-4) → **Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci[p,s]** → **Pretreatment ^{123}I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)[o,t,u]**

- **Confirmed radioiodine-avid tumor** → **RAI therapy (100–200 mCi, or dose adjusted by dosimetry)[q]; post-treatment imaging (whole body RAI scan)**
- **Cervical uptake only[p]** → **Consider RAI ablation/ adjuvant therapy (30–100 mCi)[q] post-treatment imaging (whole body RAI scan)**

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

and

Levothyroxine to appropriate TSH target See (THYR-A)

[o]While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions, the panel recommends (category 2B) selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative 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.

[p]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

[q]The administered activity of RAI therapy should be adjusted for pediatric patients.

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

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

[u]RhTSH may be used for elderly patients for when prolonged hypothyroidism may be risky.

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

SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound[v]
- 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[w]
- 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 →

Long-term surveillance

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

→ Recurrent disease See (PAP-8)

→ Abnormal findings →

Additional workup

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

→ Metastatic disease See (PAP-9)

[v] A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[w] In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging.
[x] If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH.

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

RECURRENT DISEASE

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

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

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

→ Consider radioiodine therapy with 100–150 mCi[q]
and
post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

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

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

[h] See Principles of TSH Suppression (THYR-A).
[q] The administered activity of RAI therapy should be adjusted for pediatric patients.
[y] Preoperative vocal cord assessment, if central neck recurrence.

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

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy
- **Continue to suppress TSH with levothyroxine[h]**

→ **Iodine-refractory unresectable loco-regional recurrent/persistent disease** or **Iodine-refractory soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)**
→
- **For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.[aa]**
- **While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[bb,cc,dd]**
- **Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies[ee] when available to metastatic lesions if progressive and/or symptomatic.**
- **Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[bb]** (See PAP-7)

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

→ **CNS metastases** → See (PAP-10)

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

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

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

CNS metastases →

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

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

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

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

Follicular neoplasm[a] or Follicular lesion of undetermined significance (FLUS)[a] See (THYR-3)
→ **Diagnostic procedures:**
- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- CT/MRI with contrast for fixed, bulky, or substernal lesions[b]
- Consider evaluation of vocal cord mobility (ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy)[c]

→ **Primary treatment:**

**Total thyroidectomy if invasive cancer, metastatic cancer, or patient preference
Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease**
- **Benign** → **Levothyroxine therapy to keep TSH normal[g]**
- **Papillary carcinoma** → See (PAP-3)
- **Follicular carcinoma** → See Postsurgical Evaluation (FOLL-2)

or

Lobectomy/isthmusectomy[d]
- **Invasive cancer (extensive vascular invasion)** → **Completion of thyroidectomy** → See Postsurgical Evaluation (FOLL-2)
- **• Minimally invasive cancer[e] • NIFTP pathologic diagnosis[f]** → **Completion of thyroidectomy** → See Postsurgical Evaluation (FOLL-2); **or Observe** → **Consider levothyroxine therapy to keep TSH low or normal[g]** → See Surveillance and Maintenance (FOLL-7)
- **Benign** → **Observe**
- **Papillary carcinoma** → See (PAP-2)

[a]The diagnosis of follicular carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics (category 2B) may be useful to allow reclassification of follicular lesions (follicular neoplasm or follicular lesions of undetermined significance (FLUS)) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing (category 2B) in conjunction with clinical and ultrasound features suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see (PAP-1). Use molecular markers with caution and caveat.
[b]Use of iodinated contrast is required for optimal cervical imaging using CT, although iodinated contrast will delay treatment with RAI.
[c]Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[d]RAI not recommended after lobectomy.
[e]Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion (1-4) and often requires examination of at least 10 histologic sections to demonstrate.
[f]Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), has been reclassified and only lobectomy is needed.
[g]See Principles of TSH Suppression (THYR-A).

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

POSTSURGICAL EVALUATION

- **No gross residual disease in neck** → See Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (FOLL-3)
- **Gross residual disease in neck**
  - **Resectable** → **Resect, if possible**
    - **No gross residual disease** → See Consideration for Initial Postoperative RAI Therapy After Total Thyroidectomy (FOLL-3)
    - **Gross residual disease** → see below
  - **Unresectable** → see below

Gross residual disease / **Unresectable** →
- TSH + Tg measurement + antithyroglobulin antibodies (6–12 wk postoperatively)
- Total body radioiodine imaging (category 2B)

→
- **Suspected or proven inadequate RAI uptake** → Observe or Consider EBRT/IMRT if disease is threatening vital structures
- **Adequate RAI uptake** →
  - Radioiodine treatment (preferred)
  - Post-treatment ^{131}I whole body imaging
  - Consider EBRT/IMRT
- **No RAI imaging performed** → (same as above)

→ **Suppress TSH with levo-thyroxine**[g] → See Surveillance and Maintenance (FOLL-7)

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

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

CLINICOPATHOLOGIC FACTORS | **CONSIDERATION FOR INITIAL POSTOPERATIVE RAI THERAPY AFTER TOTAL THYROIDECTOMY**

RAI not typically recommended (if all present):
- Primary tumor <2 cm
- Intrathyroidal
- No vascular invasion
- Clinical N0
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL[h]

→ RAI not typically indicated

RAI selectively recommended (if any present):
- Primary tumor 2–4 cm
- Minor vascular invasion
- Cervical lymph node metastases
- Postoperative unstimulated Tg <5–10 ng/mL[h]

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

RAI recommended (if any present):
- Gross extrathyroidal extension
- Primary tumor >4 cm
- Extensive vascular invasion
- Postoperative unstimulated Tg >5–10 ng/L[h,i]

→ RAI being considered, See (FOLL-5)

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

Gross residual disease not amenable to RAI therapy → See (FOLL-9)

[h]Tg values obtained 6–12 weeks after total thyroidectomy.
[i]Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

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

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

RAI NOT TYPICALLY INDICATED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → **Clinicopathologic findings that would not typically indicate routine RAI ablation** See (FOLL-3) → **• Unstimulated Tg • Lateral neck ultrasound if not done preoperatively** →

- **• Tg >5–10 ng/mL (with negative anti-Tg antibodies) • No concerning findings on neck ultrasound** → **• Consider additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast)** → **Consider further surgery prior to RAI** → **Consider RAI ablation/ adjuvant therapy;** See (FOLL-5)
- **Tg <5–10 ng/mL (with negative anti-Tg antibodies) No concerning finding on neck ultrasound** → **Follow without RAI ablation and** See Surveillance and Maintenance (FOLL-7) **and Levothyroxine to appropriate TSH target** See (THYR-A)
- **Clinically significant, indeterminate or suspicious cervical nodes[j]** →
  - **Benign FNA** → **Follow without RAI ablation and** See Surveillance and Maintenance (FOLL-7) **and Levothyroxine to appropriate TSH target** See (THYR-A)
  - **Malignant FNA** → **Consider further surgery prior to RAI** See (FOLL-2)

[j]For example, round morphology, calcifications, multiplicity, or growing enlarging nodes.

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

RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → Clinicopathologic findings prompting consideration for RAI, without gross residual disease or known distant metastasis See (FOLL-3) → Consider pretreatment ^{123}I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH); (category 2B)[k,l]

- No or minor thyroid bed uptake on scan, unstimulated Tg <1 ng/mL (with negative anti-Tg antibodies) → Follow without RAI ablation
- Suspected[l,m] or proven thyroid bed uptake → Follow without RAI ablation or RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)[n,o] post-treatment imaging (whole body RAI scan)
- Suspected[l,m] or proven radioiodine-avid metastatic foci → RAI therapy (100–200 mCi)[n]; post-treatment imaging (whole body RAI scan)

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

[k] Alternatively, low-dose ^{131}I (1–3 mCi) may be used.
[l] 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.
[m] Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.
[n] The administered activity of RAI therapy should be adjusted for pediatric patients.
[o] If RAI ablation is used in T1b/T2 (1–4 cm), clinical N0 disease, 30 mCi of ^{131}I is recommended (category 1) following either recombinant human TSH stimulation or thyroid hormone withdrawal. This dose of 30 mCi may also be considered (category 2B) for patients with T1b/T2 (1–4 cm) with small-volume N1a disease (fewer than 3–5 metastatic lymph node metastases <0.5 in diameter) and for patients with primary tumors <4 cm, clinical M0 with minor extrathyroidal extension.

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

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

6–12 weeks post-thyroidectomy → **Known or suspected distant metastases at presentation** See (FOLL-3) → **Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci[m,p]** → **Pretreatment ^{123}I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)[l,q,r]**

- **Confirmed radioiodine-avid tumor** → **RAI therapy (100–200 mCi, or dose adjusted by dosimetry)[s]; post-treatment imaging (whole body RAI scan)**
- **Central-cervical (remnant) uptake only** → **Consider RAI ablation/adjuvant therapy (30–100 mCi)[s]; post treatment imaging (whole body RAI scan)**

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

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

[m]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.

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

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

[r]rhTSH may be used for elderly patients for whom prolonged hypothyroidism may be risky.

[s]The administered activity of RAI therapy should be adjusted for pediatric patients.

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

SURVEILLANCE AND MAINTENANCE | **FINDINGS** | **MANAGEMENT**

Surveillance and maintenance:

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

Findings: NED → **Long-term surveillance**

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

→ Recurrent disease (See FOLL-8)

Findings: Abnormal findings → **Additional workup**

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

→ Metastatic disease (See FOLL-9)

[t] A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[u] In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging
[v] If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH.

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

RECURRENT DISEASE

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

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

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

→ Consider radioiodine therapy with 100–150 mCi[n] and post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

Locoregional recurrence → Surgery (preferred) if resectable[w]
and/or
Radioiodine treatment,[n]
if radioiodine imaging positive
and/or
local therapies when available (ethanol ablation, RFA)
and/or
EBRT/IMRT, if radioiodine imaging negative for select patients not responsive to other therapies
or
observation for low-volume disease that is stable and distant from critical structures

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

[g]See Principles of TSH Suppression (THYR-A).
[n]The administered activity of RAI therapy should be adjusted for pediatric patients.
[w]Preoperative vocal cord assessment, if central neck recurrence.

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

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy
- **Continue to suppress TSH with levothyroxine[g]**

→ **Iodine-refractory unresectable loco-regional recurrent/persistent disease** or **Iodine-refractory soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)**
- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.[y]
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[z,aa,bb]
- Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies[cc] when available to metastatic lesions if progressive and/or symptomatic.
- Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[z] (See FOLL-7)

→ **Iodine-refractory metastatic bone metastases[x]**
- Consider surgical palliation and/or EBRT/SBRT/other local therapies[cc] 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.[x]
- Active surveillance may be appropriate in asymptomatic patients with indolent disease.[z] (See FOLL-7)
- For progressive and/or symptomatic disease, consider lenvatinib (preferred) or sorafenib.[y] While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.[z,aa,bb]

→ **CNS metastases** → See (FOLL-10)

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

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

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

CNS metastases →

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

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

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

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

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

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

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

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

Hürthle cell neoplasm[a] (See THYR-3) →

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

→

Total thyroidectomy if invasive cancer, metastatic disease, or patient preference
Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease
- → Benign → Levothyroxine therapy to keep TSH normal[h]
- → Hürthle cell carcinoma[g] → See Postsurgical Evaluation (HÜRT-2)

or

Lobectomy/isthmusectomy[d]
- → Invasive cancer (extensive vascular invasion) → Completion of thyroidectomy → See Postsurgical Evaluation (HÜRT-2)
- → • Minimally invasive cancer[e] • NIFTP pathologic diagnosis[f] →
  - Completion of thyroidectomy → See Postsurgical Evaluation (HÜRT-2)
  - or
  - Observe → Consider levothyroxine therapy to keep TSH low or normal[h] → See Surveillance and Maintenance (HÜRT-7)
- → Benign → Observe

[a]The diagnosis of Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA.
[b]Use of iodinated contrast is required for optimal cervical imaging using CT, although iodinated contrast will delay treatment with RAI.
[c]Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[d]RAI not recommended after lobectomy.
[e]Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci (1-4) of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.
[f]Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been reclassified and only lobectomy is needed.
[g]Also known as oxyphilic, oncocytic, or follicular carcinoma, oncocytic type.
[h]See Principles of TSH Suppression (THYR-A).

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

POSTSURGICAL EVALUATION

- **No gross residual disease in neck** → See Consideration for Initial Postoperative RAI Therapy (HÜRT-3)
- **Gross residual disease in neck**
  - **Resectable** → **Resect, if possible**
    - **No gross residual disease** → See Consideration for Initial Postoperative RAI Therapy (HÜRT-3)
    - **Gross residual disease**
  - **Unresectable**

Gross residual disease / Unresectable →

- **TSH + Tg measurement + antithyroglobulin antibodies (6–12 wk postoperatively)**
- **Total body radioiodine imaging (category 2B)**

→

- **Suspected or proven inadequate RAI uptake** → **Observe or Consider EBRT/IMRT if disease is threatening vital structures** → Suppress TSH with levothyroxine[h]
- **Adequate RAI uptake** or **No RAI imaging performed** →
  - **Radioiodine treatment (preferred)**
  - **Post-treatment ^{131}I whole body imaging**
  - **Consider EBRT/IMRT**

  → **Suppress TSH with levothyroxine[h]** → See Surveillance and Maintenance (HÜRT-7)

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

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

CLINICOPATHOLOGIC FACTORS | **CONSIDERATION FOR INITIAL POSTOPERATIVE RAI THERAPY**

RAI not typically recommended (if all present):
- Primary tumor <2 cm
- Intrathyroidal
- No vascular invasion
- Clinical N0
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg <1 ng/mL[i]

→ RAI not typically indicated See (HÜRT-4)

RAI selectively recommended (if any present):
- Primary tumor 2–4 cm
- Minor vascular invasion
- Cervical lymph node metastases
- Postoperative unstimulated Tg <5–10 ng/mL[i]

→ 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-5)

RAI recommended (if any present):
- Gross extrathyroidal extension
- Primary tumor >4 cm
- Extensive vascular invasion
- Postoperative unstimulated Tg >5–10 ng/L[i,j]

→ RAI being considered See (HÜRT-5)

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

Gross residual disease not amenable to RAI therapy → See (HÜRT-9)

[i]Tg values obtained 6–12 weeks after total thyroidectomy.
[j]Additional cross-sectional imaging (CT or MRI of the neck with contrast and chest CT with contrast) should be considered to rule out the presence of significant normal thyroid remnant or gross residual disease and to detect clinically significant distant metastases.

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

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

RAI NOT TYPICALLY INDICATED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → **Clinicopathologic findings that would not typically indicate routine RAI ablation** (See HÜRT-3) →
- **Unstimulated Tg**
- **Lateral neck ultrasound if not done preoperatively**

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

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

→ **Tg <5–10 ng/mL (with negative anti-Tg antibodies)**
No concerning finding on neck ultrasound
→ **Follow without RAI ablation and** See Surveillance and Maintenance (HÜRT-7) **and Levothyroxine to appropriate TSH target** (See THYR-A)

→ **Clinically significant, indeterminate, or suspicious cervical nodes**[k]
- → **Benign FNA** → **Follow without RAI ablation and** See Surveillance and Maintenance (HÜRT-7) **and Levothyroxine to appropriate TSH target** (See THYR-A)
- → **Malignant FNA** → **Consider further surgery prior to RAI;** See (HÜRT-2)

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

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

RAI BEING CONSIDERED BASED ON CLINICOPATHOLOGIC FEATURES

6–12 weeks post-thyroidectomy → **Clinicopathologic findings prompting consideration for RAI, without gross residual disease or known distant metastasis** (See HÜRT-3) → **Consider pretreatment ^{123}I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH); (category 2B)[l,m]**

- **No or minor thyroid bed uptake on scan, unstimulated Tg <1 ng/mL (with negative anti-Tg antibodies)** → **Follow without RAI ablation**
- **Suspected[m,n] or proven thyroid bed uptake** → **Follow without RAI ablation or RAI for remnant ablation (30–50 mCi) or adjuvant therapy (50–100 mCi)[o,p] post-treatment imaging (whole body RAI scan)**
- **Suspected[m,n] or proven radioiodine avid metastatic foci** → **RAI therapy (100–200 mCi)[o]; post-treatment imaging (whole body RAI scan)**

All of the above → **See Surveillance and Maintenance (HÜRT-7)** **and Levothyroxine to appropriate TSH target** **(See THYR-A)**

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

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

KNOWN OR SUSPECTED DISTANT METASTATIC DISEASE

6–12 weeks post-thyroidectomy → **Known or suspected distant metastases at presentation** (See HÜRT-3) → **Appropriate cross-sectional imaging (CT or MRI with contrast) of known metastatic foci**[n,q] → **Pretreatment ^{123}I diagnostic imaging with TSH stimulation (thyroid hormone withdrawal or rhTSH)**[r,s,t] →

- **Confirmed radioiodine avid tumor** → **RAI therapy (100–200 mCi, or dose adjusted by dosimetry)**[o]**; post treatment imaging (whole body RAI scan)**
- **Central-cervical (remnant) uptake only** → **Consider RAI ablation/adjuvant therapy (30–100 mCi)**[o]**; post treatment imaging (whole body RAI scan)**

→ **See Surveillance and Maintenance (HÜRT-7)** **and Levothyroxine to appropriate target** (See THYR-A)

[n]Clinically significant structural disease should be surgically resected if possible before radioiodine treatment.
[o]The administered activity of RAI therapy should be adjusted for pediatric patients.
[q]To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression.
[r]If ^{123}I is not available, low-dose ^{131}I(1-3 mCi) may be used. Dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis.
[s]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 of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Dialysis patients require special handling.
[t]rhTSH 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SURVEILLANCE AND MAINTENANCE | **FINDINGS** | **MANAGEMENT**

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

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

→ Recurrent disease (See HÜRT-8)

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

→ Metastatic disease (See HÜRT-9)

[u]A subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[v]In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging.
[w]If there is a high likelihood of therapy, thyroid hormone withdrawal is suggested; if not, suggest using rhTSH.

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

RECURRENT DISEASE

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

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

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

→ Consider radioiodine therapy with 100–150 mCi[o]
and
post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy

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

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

[h]See Principles of TSH Suppression (THYR-A).
[o]The administered activity of RAI therapy should be adjusted for pediatric patients.
[x]Preoperative vocal cord assessment, if central neck recurrence.

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

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy
- **Continue to suppress TSH with levothyroxine[h]**

→ **Iodine-refractory unresectable loco-regional recurrent/persistent disease** or **Iodine-refractory soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)** →
- **For progressive and/or symptomatic disease, consider lenvatinib (preferred), or sorafenib.[z]**
- **While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[aa,bb,cc]**
- **Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies[dd] when available to metastatic lesions if progressive and/or symptomatic.**
- **Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[aa]** (HÜRT-7)

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

→ **CNS metastases** → See (HÜRT-10)

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

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

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

CNS metastases →

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

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

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

CLINICAL PRESENTATION	DIAGNOSTIC PROCEDURES		PRIMARY TREATMENT	
Medullary thyroid carcinoma on FNA →	• Basal serum calcitonin level • CEA • Pheochromocytoma screening[b] • Serum calcium • Consider genetic counseling • Screen for RET proto-oncogene mutations[c] (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)[d] • Consider contrast-enhanced CT of chest and liver MRI or 3-phase CT with contrast of liver[e,f]	≥1.0 cm in diameter or bilateral thyroid disease →	• Total thyroidectomy with bilateral central neck dissection (level VI) • Therapeutic ipsilateral or bilateral modified neck dissection for clinically or radiologically identifiable disease (levels II–V) • Consider prophylactic ipsilateral modified neck dissection for high-volume or gross disease in the adjacent central neck • Consider therapeutic EBRT/IMRT for grossly incomplete tumor resection when additional attempts at surgical resection have been ruled out • Adjuvant EBRT/IMRT is rarely recommended • Postoperative administration of levothyroxine to normalize TSH	→ See Management 2–3 Months Postoperative (MEDU-5)
		<1.0 cm in diameter and unilateral thyroid disease →	Total thyroidectomy and consider neck dissection (level VI)	→ See Management 2–3 Months Postoperative (MEDU-5)
Medullary thyroid carcinoma diagnosed after initial thyroid surgery →				See Additional Workup and Management (MEDU-2)
Germline mutation of RET proto-oncogene[a,b] →				See Additional Workup and Primary Treatment (MEDU-3)

[a]In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[b]Evidence of pheochromocytoma should be evaluated and addressed appropriately before proceeding to the next step on the pathway.
[c]Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors).
[d]Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[e]Having distant metastases does not mean that surgery is contraindicated.
[f]Liver imaging is seldom needed if calcitonin <400 pg/mL.

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

CLINICAL PRESENTATION	ADDITIONAL WORKUP		MANAGEMENT
Medullary thyroid carcinoma diagnosed after initial thyroid surgery[g] →	• Basal serum calcitonin level • CEA • Screen for germline RET proto-oncogene mutations[c] (exons 10, 11, 13–16) • Consider 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)

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

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

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

CLINICAL PRESENTATION		ADDITIONAL WORKUP	PRIMARY TREATMENT	
Germline mutation of RET proto-oncogene[a,c]	MEN 2B (codon 918, 883, or compound heterozygous [V804M + E805K, Y806C, or S904C] RET mutations)[h]	• Basal serum calcitonin level[i] • CEA • Pheochromocytoma screening[b,j] • Central and lateral neck compartments ultrasound, if not previously done	• Total thyroidectomy during the first year of life or at diagnosis[a] • Therapeutic neck dissection as indicated; consider prophylactic bilateral central neck dissection (level VI) • Consider more extensive node dissection (levels II–V) if tumor(s) >0.5 cm in diameter • Adjuvant EBRT/IMRT is rarely recommended • Postoperative administration of levothyroxine to normalize TSH	See Management 2–3 Months Postoperative (MEDU-5)
	MEN 2A/Familial medullary thyroid carcinoma (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations)[h]	• Basal serum calcitonin level[i] • CEA • Pheochromocytoma screening[b,j] • Serum calcium ± parathyroid hormone [PTH]) • Central and lateral neck compartments ultrasound, if not previously done		See Primary Treatment (MEDU-4)

[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[b] Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.
[c] Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)
[h] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less high risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)
[i] Normal calcitonin ranges have not been established for very young children.
[j] Screening for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A) should be performed annually. For some RET mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.

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

CLINICAL PRESENTATION

MEN 2A/Familial medullary thyroid carcinoma (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations)[a,c,h] → Measure serum calcium ± PTH

PRIMARY TREATMENT

No primary hyperparathyroidism →
- Total thyroidectomy by age 5[a,h] or when mutation identified[a] (if mutation identified at older age)
- Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin[k] or CEA test or ultrasound identified thyroid or nodal abnormality
- Consider prophylactic ipsilateral modified neck dissection if there is high-volume or gross disease in the adjacent central neck
- Consider more extensive lymph node dissection (levels II–V) if tumor(s) >1.0 cm or central node(s) positive
- Adjuvant EBRT/IMRT is rarely recommended
- Postoperative administration of levothyroxine to normalize TSH

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

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

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

[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[c] Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Guidelines for Neuroendocrine Tumors)
[h] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation. Codon 634 mutations are considered highest risk with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally lower risk. Prophylactic thyroidectomy may be delayed in patients with less-high-risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)
[k] Prophylactic neck dissection may not be required if serum calcitonin is less than 40 ng/mL, because lymph node metastases are unlikely with minor calcitonin elevations in this setting.

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

MANAGEMENT 2–3 MONTHS POSTOPERATIVE | **SURVEILLANCE**

- Basal calcitonin
- CEA

→ **Detectable basal calcitonin or Elevated CEA** →
- Neck ultrasound
- If calcitonin ≥150 pg/mL, cross-sectional imaging should include contrast-enhanced CT (± PET) or MRI with contrast of the neck, chest, abdomen with liver protocol[m]
- Bone scan in select patients[m]

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

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

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

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

→ **Basal calcitonin undetectable and CEA within reference range[l]** → **Observe** →
- Annual serum calcitonin, CEA
- Consider central and lateral neck compartments ultrasound
- Additional studies or more frequent testing if significantly rising calcitonin or CEA
- No additional imaging required if calcitonin and CEA stable
- For MEN 2B or 2A, annual biochemical screenings for pheochromocytoma and hyperparathyroidism (MEN 2A)[n]

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

  → **Negative result** → Continue observation

[l] The likelihood of significant residual disease with an undetectable basal calcitonin is very low.
[m] Bone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.
[n] See page (PHEO-I) from the NCCN Guidelines for Neuroendocrine Tumors.

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

RECURRENT OR PERSISTENT DISEASE
LOCOREGIONAL DISEASE

TREATMENT

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

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

[o]Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[p]Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.
[q]Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).
[r]Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.

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

RECURRENT OR PERSISTENT DISEASE
DISTANT METASTASES

Asymptomatic disease → **Observe or Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy), or vandetanib[o,p] (category 1), or cabozantinib[o] (category 1) if not resectable and progressing by RECIST criteria[q,r]** → **Progressive disease, see pathway below**

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

[o]Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[p]Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.
[q]Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).
[r]Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.
[s]Clinical benefit can be seen in both sporadic and familial MTC.
[t]While not FDA approved for treatment of medullary thyroid cancer, other commercially available small-molecule kinase inhibitors (such as sorafenib, sunitinib, lenvatinib, or pazopanib) can be considered if clinical trials, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib.
[u]Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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

FNA OR CORE BIOPSY FINDING[a]

Anaplastic thyroid carcinoma (ATC) →

DIAGNOSTIC PROCEDURES

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

→

ESTABLISH GOALS OF THERAPY[b]

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

STAGE[c]

Stage IVA or IVB[a,b] (Locoregional disease)
- R0/R1 resection[e] achieved (usually as incidentally discovered, very small ATC) → Adjuvant EBRT/IMRT ± Chemotherapy[f]
- Incomplete (R2 resection)/Unresectable[e] → EBRT/IMRT ± Chemotherapy[f] → Surgery can be reconsidered after neoadjuvant therapy depending on response

Stage IVC (metastatic disease)[b] → See (ANAP-2)

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

[b]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.

[c]See Staging (ST-1).

[d]Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.

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

[f]See Systemic Therapy for Anaplastic Thyroid Carcinoma (ANAP-A).

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

METASTATIC DISEASE | **TREATMENT** | **SURVEILLANCE AND MANAGEMENT**

Stage IVC[c]

- Aggressive therapy →
  - Total thyroidectomy with therapeutic lymph node dissection if resectable (R0/R1)
  - Locoregional radiation therapy
  - Systemic therapy (See ANAP-A)
  - Consider clinical trial
- Palliative care →
  - Palliative locoregional radiation therapy
  - Local lesion control with surgery or radiation (eg, bone[g], brain metastases)
  - See NCCN Guidelines for Central Nervous System Cancers
  - Hospice/Best supportive care

→

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

→

- Continued observation if NED
- Palliative locoregional radiation therapy
- Local lesion control (eg, bone[g], brain metastases)
- Second-line systemic therapy or clinical trial
- See NCCN Guidelines for Palliative Care
- Hospice/Best supportive care

[c]See Staging (ST-1).
[g]Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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

SYSTEMIC THERAPY[1]

Regimen	Agents/Dosages	Frequency
Paclitaxel/carboplatin	Paclitaxel 60–100 mg/m^2, carboplatin AUC 2 mg/m^2 IV	Weekly
Paclitaxel/carboplatin	Paclitaxel 135–175 mg/m^2, carboplatin AUC 5–6 mg/m^2 IV	Every 3–4 weeks
Docetaxel/doxorubicin	Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (with pegfilgrastim) or Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Every 3–4 weeks Weekly
Paclitaxel	60–90 mg/m^2 IV	Weekly
Paclitaxel	135–200 mg/m^2 IV	Every 3–4 weeks
Doxorubicin	60–75 mg/m^2 IV	Every 3 weeks
Doxorubicin	20 mg/m^2 IV	Weekly

[1]Reprinted 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Primary Tumor (T)

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

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 2 cm or less in greatest dimension limited to the thyroid
T1a *Tumor 1 cm or less, limited to the thyroid*
T1b Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3 Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4a Moderately advanced disease
Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b Very advanced disease
Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel

All anaplastic carcinomas are considered T4 tumors.

T4a Intrathyroidal anaplastic carcinoma
T4b Anaplastic carcinoma with gross extrathyroid extension

Regional Lymph Nodes (N)

Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
N1a Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Residual Tumor (R)

Classification of relevance to assess impact of surgery on outcomes:

R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor
Rx Presence of residual tumor cannot be determined

Stage grouping:
Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma.

Papillary or Follicular (differentiated)
Under 45 Years

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

Papillary or Follicular
45 Years and Older

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

Medullary Carcinoma (all age groups)

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

Anaplastic Carcinoma
All anaplastic carcinomas are considered Stage IV

Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Epidemiology

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

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%.[7] It is estimated that approximately 56,870 new cases of thyroid carcinoma will be diagnosed in the United States in 2017.[8] As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men. Thyroid carcinoma is currently the fifth most common malignancy diagnosed in women.[8] The disease is also diagnosed more often in white North Americans than in African Americans. Although thyroid carcinoma can occur at any age, the peak incidence is approximately age 50 years.[7]

The main histologic types of thyroid carcinoma are: 1) differentiated (including papillary, follicular, and Hürthle cell); 2) medullary; and 3) anaplastic, which is an aggressive undifferentiated tumor. An average of 63,229 patients per year were diagnosed with thyroid carcinoma from 2010 to 2014. Of these 63,229 patients, 89.4% had papillary carcinoma, 4.6% had follicular carcinoma, 2.0% had Hürthle cell carcinoma, 1.7% had medullary carcinoma, and 0.8% had anaplastic carcinoma.[7] The 5-year relative survival rates for patients with papillary and follicular carcinomas (stages I–III) were 98% and 90%, respectively.[9,10]

In 2017, it is estimated that approximately 2010 cancer deaths will occur among persons with thyroid carcinoma in the United States.[8] Anaplastic carcinoma is almost uniformly lethal; however, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases. Thyroid carcinoma occurs more often in women; however, mortality rates are lower for younger women.[7,11-13] Although the estimated incidence of thyroid carcinoma previously increased by an average of ~5% annually between 2004 and 2013, the incidence rate has recently stabilized, likely due to more conservative indications for thyroid biopsy.[8] Because overall mortality has not dramatically increased since 1975 (1150 vs. 2010 deaths), the previous increase in incidence may reflect, at least in part, earlier detection of subclinical disease (ie, small papillary carcinomas).[14-19] However, data show the incidence has increased by varying degrees across all tumor sizes and age groups.[20-29] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[7,30,31]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma address management for the different types of thyroid carcinoma including papillary, follicular, Hürthle cell, medullary, and anaplastic carcinoma. Additional sections in these NCCN Guidelines® include *Nodule Evaluation, Principles of Thyroid-Stimulating Hormone (TSH) Suppression, Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma,* and the AJCC staging tables.[9] This Discussion text describes the recommendations in the algorithm in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithm. These NCCN Guidelines for Thyroid

Carcinoma are updated at least once a year and are available at NCCN.org. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the NCCN Panel during the process of developing these guidelines.

Literature Search Criteria and Guidelines Update Methodology

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

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

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

Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma can be a challenge, because until recently, few prospective randomized trials of treatment have been done.[32,33] Most of the information about treatment comes from studies of large cohorts of patients for whom therapy has not been randomly assigned. This accounts for much of the disagreement about managing differentiated carcinoma. Nonetheless, most patients can be cured of this disease when properly treated by experienced physicians and surgeons.[34] The treatment of choice is surgery, followed by radioactive iodine (RAI) ablation (131I) in selected patients and thyroxine therapy in most patients.

Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma.[35] The thyroid glands of children are especially vulnerable to ionizing radiation. A child's thyroid gland has one of the highest risks of developing cancer of any organ. The thyroid gland is the only organ linked to risk at about 0.10 Gy.[5] The risk for radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma.[36] These data suggest that genetic factors are also important in the development of thyroid carcinoma. Beginning within 5 years of irradiation during childhood, new nodules develop at a rate of about 2% annually, reaching a peak incidence within 30 years of irradiation but remaining high at 40 years.[5,6]

Adults have a very small risk of developing thyroid carcinoma after exposure to 131I.[37] After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary carcinomas after being exposed to 131I fallout.[38] It became evident that 131I and other short-lived 131Is were potent thyroid carcinogens in these children, particularly those younger than 10 years of age when they were exposed.[39] Iodine deficiency increases the risk for radiation-induced thyroid cancer.[40] Although radiation-induced papillary carcinoma tends to appear more aggressive histologically and to have high recurrence rates, the prognosis for survival is similar to that of spontaneously occurring tumors.[41-43] Iodine deficiency is associated with follicular carcinoma and anaplastic carcinomas.

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. However, evaluating all nodules for malignancy is difficult, because benign nodules are so prevalent and because thyroid carcinoma is so uncommon.[1,44,45] Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their diagnosis. About 50% of the malignant nodules are discovered during a routine physical examination, by serendipity on imaging studies, or during surgery for benign disease. The other 50% are usually first noticed by the patient, usually as an asymptomatic nodule.[1,44] Regrettably, the typically indolent nature of differentiated thyroid carcinoma often leads to long delays in diagnosis that may substantially worsen the course of the disease.[12]

Initial Workup

For a patient with a thyroid nodule, the first step is to measure the serum thyrotropin (thyroid-stimulating hormone [TSH]) level and to do an ultrasound of the thyroid and neck; all nodules (even incidentalomas) should have this assessment; there is no size cutoff.[3,46-48] The TSH level, ultrasound results, and clinical features are used to determine whether is it necessary to do fine-needle aspiration (FNA) of the nodule or whether there is a low risk of malignancy (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[45,49]

FNA, with or without ultrasound guidance, is the procedure of choice for evaluating suspicious thyroid nodules.[3,45,50] Data show that higher TSH levels are associated with an increased risk for differentiated thyroid carcinoma in patients with thyroid nodules, although TSH and thyroglobulin (Tg) do not appear to be useful for screening for thyroid cancer.[51-54] FNA should be considered in patients with normal or elevated TSH, certain ultrasound features, and clinical findings. FNA of clinically significant or suspicious cervical lymph nodes should also be considered if identified in the ultrasonographic evaluation of the thyroid and neck. Ultrasound features that increase the threshold for FNA are described in the NCCN algorithm (see *Sonographic Features* in *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). RAI imaging is recommended in patients with low TSH.

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

In the setting of a multinodular thyroid gland, selection of nodules for FNA should be based on the pattern of radiographic features that predict a higher likelihood of malignancy, such as the previous example, or based on growth of a nodule over time. Similarly, choosing which nodules are appropriate for active surveillance rather than FNA should be based on the pattern of ultrasound features that predict benignity (eg, spongiform appearance, a pure cyst, specific intranodular appearances) or small size due to treatment considerations as previously noted.[55,56,61] At the time of thyroid ultrasound, a critical feature that should be assessed is the presence or absence of concerning lymphadenopathy in the central and lateral neck. The presence of a node with concerning characteristics (eg, hypoechoic, rounded, absent of fatty hilum, cystic or partially cystic, microcalcifications) should lead to FNA of the node rather than, or in addition to, the most concerning thyroid nodule.

Thyroid nodules smaller than 1 cm occur with such frequency in the asymptomatic general population that they are often found by serendipity when performing imaging studies for other head or neck problems.[17,62] Often termed “incidentalomas,” nodules smaller than 1 cm are typically clinically insignificant lesions and usually do not require FNA, unless there are suspicious findings (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[4,14,47,63-67] In selected cases, it may be reasonable to follow these nodules with serial ultrasounds. Data indicate that older patients with intrathyroidal papillary microcarcinomas may be good candidates for an active surveillance approach (rather than immediate surgery) and usually show no evidence of clinically significant disease progression over at least 5 to 10 years of follow-up.[68] These observations cast doubt on the clinical benefit of diagnosing (and treating) papillary microcarcinoma in these selected groups.[69] Others feel that surgery should be considered for select patients with papillary carcinomas who are 45 years of age or older.[70]

The NCCN Panel uses recommendations from several organizations (eg, American Thyroid Association [ATA], Society of Radiologists in Ultrasound, NCI) and their expertise when formulating the NCCN Guidelines for thyroid nodules (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[3,49,71] The NCCN recommendations describe which nodules require further assessment with FNA and which can undergo active surveillance. In 2015, the ATA updated its guidelines on the management of thyroid nodules and thyroid cancer; its comprehensive guidelines also discuss ultrasound and FNA.[72] In 2007, the NCI had a conference on using FNA to manage thyroid nodules. The NCI guidelines discuss which nodules should undergo FNA and discuss the FNA results (ie, carcinoma, benign).[45,49] The Society of Radiologists in Ultrasound wrote a consensus statement in 2005 about management of thyroid nodules identified at thyroid ultrasonography. Its recommendations describe which nodules should undergo FNA based on nodule size and ultrasound characteristics, and on clinical features that might predict risk of morbidity from an undiagnosed malignancy.[71] Suspicious criteria by ultrasound include increased central hypervascularity, hypoechoic mass, microcalcifications, infiltrative margins, and other features (see *Sonographic Features* in *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present (see *Nodule Evaluation* in the

NCCN Guidelines for Thyroid Carcinoma).[73,74] For example, the likelihood that a nodule is malignant increases about 7-fold if it is very firm, fixed to adjacent structures, rapidly growing, associated with enlarged regional lymph nodes, causes vocal cord paralysis, or symptoms of invasion into neck structures are present.[74,75] Family history of thyroid cancer is also indicative of malignancy. If 2 or more of these features are present, the likelihood of thyroid cancer is virtually assured; however, this is a rare situation.[75] A patient's age and gender also affect the probability of malignancy. Other factors that increase the suspicion of malignancy include: 1) a history of head and neck irradiation; 2) a history of diseases associated with thyroid carcinoma, such as familial adenomatous polyposis (formerly called Gardner's syndrome), Carney complex, Cowden's syndrome, and multiple endocrine neoplasia (MEN) types 2A or 2B; 3) evidence of other thyroid cancer–associated diseases or syndromes, such as hyperparathyroidism, pheochromocytoma, marfanoid habitus, and mucosal neuromas (suggestive of MEN2B), which make the presence of medullary carcinoma more likely; or 4) the presence of suspicious findings detected by imaging, such as focal FDG uptake on PET or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.[3,76]

Some clinicians, especially in Europe,[77] recommend obtaining serum calcitonin levels from all patients with thyroid nodules to assess for medullary carcinoma. However, this is controversial in the United States, especially in the absence of confirmatory pentagastrin stimulation testing and because it may not be cost effective. The ATA is equivocal about measuring serum calcitonin to screen all patients with thyroid nodules for medullary carcinoma.[3] A study showed that calcitonin screening may be cost effective in the United States.[78] However, false-positive calcitonin readings that can result from minimal calcitonin elevations have traditionally been ruled out with pentagastrin testing, and pentagastrin is not available in the United States. Some authors have suggested high-dose calcium infusion as an alternative to pentagastrin stimulation testing in patients with minimal calcitonin elevations.[79]

FNA Results

Cytologic examination of an FNA specimen is typically categorized as: 1) carcinoma (papillary, medullary, or anaplastic) or suspicious for carcinoma; 2) follicular or Hürthle cell neoplasm; 3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); 4) thyroid lymphoma; 5) benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis); or 6) insufficient biopsy (nondiagnostic) (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma). These diagnostic categories for FNA results reflect the NCI's state of the science conference held in 2007.[45,49,80] Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in the diagnosis of thyroid disorders. Although FNA is a very sensitive test—particularly for papillary carcinoma—false-negative results are sometimes obtained; therefore, a reassuring FNA should not override worrisome clinical or radiographic findings.[81,82]

Molecular diagnostic testing to detect individual mutations (eg, BRAF V600E, RET/PTC, RAS, PAX8/PPAR [peroxisome proliferator-activated receptors] gamma) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions.[83-91] The BRAF V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation.[92] Although controversial, data suggest that BRAF V600E mutations may predict for increased recurrence of papillary carcinoma.[92-96] The choice of the precise molecular test depends on the cytology and the clinical question being asked.[97-100] Indeterminate groups include: 1) follicular or Hürthle cell neoplasms; and 2) AUS/FLUS.[101-103] The NCCN Panel recommends molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[104,105] Molecular diagnostic testing is not recommended for suspected Hürthle cell neoplasms. Molecular diagnostic testing may include multigene assays (eg, the gene expression classifier) or individual mutational analysis. The gene expression classifier measures the expression of at least 140 genes.[84,106,107] BRAF V600E mutation analysis was recommended by some panelists for the evaluation of thyroid nodules (not restricted to the follicular lesions). Furthermore, a majority of the panelists would recommend BRAF V600E testing in the evaluation of follicular lesions. A minority of panelists expressed concern regarding observation of follicular lesions because they were perceived as potentially pre-malignant lesions with a very low, but unknown, malignant potential if not surgically resected (leading to recommendations for either observation or considering lobectomy in lesions classified as benign by molecular testing). Clinical risk factors, sonographic patterns, and patient preference can help determine whether observation or lobectomy is appropriate for these patients (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).

Rather than proceeding to immediate surgical resection to obtain a definitive diagnosis for these indeterminate FNA cytology groups (follicular lesions), patients can be followed with observation if the application of a specific molecular diagnostic test (in conjunction with clinical and ultrasound features) results in a predicted risk of malignancy that is comparable to the rate seen in cytologically benign thyroid FNAs (approximately ≤5%). It is important to note that the predictive value of molecular diagnostics may be significantly influenced by the pre-test probability of disease associated with the various FNA cytology groups. Furthermore, in the cytologically indeterminate groups, the risk of malignancy for FNA can vary widely between institutions.[80,108-110] Because the published studies have focused primarily on adult patients with thyroid nodules, the diagnostic utility of molecular diagnostics in pediatric patients remains to be defined. Therefore, proper implementation of molecular diagnostics into clinical care requires an understanding of both the performance characteristics of the specific molecular test and its clinical meaning across a range of pre-test disease probabilities.[105,111]

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of medullary carcinoma.[49] Hürthle cell neoplasms can sometimes mimic medullary carcinoma cytologically and on frozen section. Sometimes it can be difficult to discriminate between anaplastic carcinoma and other primary thyroid malignancies (ie, medullary carcinoma, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[112] Metastatic renal carcinoma can mimic follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma.[49] Pathology synoptic reports (protocols), such as those from the College of American Pathologists (CAP), are useful for reporting results from examinations of surgical specimens. The CAP protocol was updated in January 2016 and reflects the 2010 staging (7th edition) from the AJCC (see *Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland* on the CAP website).[9,113]

Follicular and Hürthle cell carcinomas are rarely diagnosed by FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.[34,45,81,114] 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.[115] Approximately 20% of these lesions are malignant.[74] Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful for follicular cell carcinomas (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[73,105,116]

In some patients with follicular lesions, serum TSH level and thyroid 123I or 99m technetium scanning may identify patients with an autonomously functioning or "hot" nodule who often may be spared surgery, because the diagnosis of follicular adenoma (ie, benign) is highly likely.[3,117] Patients who are clinically euthyroid with a low TSH and a hot nodule on thyroid imaging should be evaluated and treated for thyrotoxicosis as indicated even when cytology is suspicious for follicular neoplasm. Those with a hypofunctional (cold or warm) nodule and with suspicious clinical and sonographic features should proceed to surgery (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[2,3] Those patients with an increased or normal TSH and with cytology suspicious for follicular or Hürthle cell neoplasm should undergo diagnostic lobectomy or total thyroidectomy, depending on patient preference unless molecular diagnostic testing predicts a low risk of malignancy.

In patients with follicular or Hürthle cell neoplasm on FNA who are selected for thyroid surgery in order to obtain a definitive diagnosis, total thyroidectomy is recommended for bilateral disease, unilateral disease greater than 4 cm (especially in men), invasive cancer, metastatic cancer, or if the patient prefers this approach. An FNA that yields insufficient cellular material for diagnosis and is solid should be repeated, because approximately 50% of subsequent specimens are adequate to assign a diagnosis (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[74] Data suggest that ultrasound-guided FNA may be useful in diagnosing thyroid carcinoma, especially when repeating an FNA for a previously nondiagnostic biopsy.[3,118] In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.[119] Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of significant growth.[74] Significant nodule growth is defined as a greater than 50% increase in nodule volume or 20% increase in size of 2-3 dimensions.[120] 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.[12] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[121,122] In one large study, central neck recurrences were seen most often in the cervical lymph nodes (74%), followed by the thyroid remnant (20%), and then the trachea or muscle (6%). Of the group with local recurrences, 8% eventually died of cancer.[12] Distant metastases were the sites of recurrence in 21% of patients in this cohort, most often (63%) in the lungs alone. Of the patients with distant metastases, 50% died of cancer.[12]

It is important to recognize that the poor outcomes in this study were probably related to the manner in which the recurrence was diagnosed. In the past, disease recurrence was heralded by symptoms or palpable disease on physical examination, reflecting relatively large-volume disease recurrence. However, tools that are highly sensitive for detecting disease (eg, sensitive Tg assays, high-resolution neck ultrasound) appear to have resulted in earlier detection of disease recurrence, which is now often found in the first 2 to 5 years of follow-up.[3,123] 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.[124,125]

Prognosis

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular carcinomas, patient age at the time of initial therapy and tumor stage are important.[12,126-128] 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.[12,126-129] 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.[130,131] 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.[132] 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.[133-135] However, most physicians treating the disease believe that tumor stage and its histologic features should be as significant as the patient's age in determining management.[12,130,136,137] Prognosis is less favorable in men than in women, but the difference is usually small.[12,135] One study found that gender was an independent prognostic variable for survival and that the risk of death from cancer was about twice as high in men as in women.[12] Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.[138]

Familial Syndromes

Familial, non-medullary carcinoma accounts for about 5% of papillary thyroid carcinoma (PTCs) and, in some cases, may be clinically more aggressive than the sporadic form.[139,140] 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.[141]

Other familial syndromes associated with papillary carcinoma are familial adenomatous polyposis,[142] Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands),[143] and Cowden's syndrome (multiple hamartomas).[144] 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.[129,145-147] The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, BRAF V600E mutation status, and metastases.[148-150] For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.[3,151-154] 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).[113] In patients with sporadic medullary carcinoma, a somatic RET oncogene mutation confers an adverse prognosis.[155]

Histology

Although survival rates with typical papillary carcinoma are quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors.[1] A well-defined tumor capsule, which is found in about 10% of PTCs, is a particularly favorable prognostic indicator. A worse prognosis is associated with: 1) anaplastic tumor transformation; 2) tall-cell papillary variants, which have a 10-year mortality of up to 25%; 3) columnar variant papillary carcinoma (a rapidly growing tumor with a high mortality rate); and 4) diffuse sclerosing variants, which infiltrate the entire gland.[34,156]

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), formerly known as encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), is characterized by its follicular growth pattern, encapsulation or clear demarcation of the tumor from adjacent tissue with no invasion, and nuclear features of papillary carcinoma.[157,158] NIFTP tumors have a low risk for adverse outcomes and, therefore, require less aggressive treatment.[158-161] NIFTP was re-classified to prevent overtreatment of this indolent tumor type as well as the psychological consequences of a cancer diagnosis on the patient.[157,158] Molecular diagnostic testing may be useful for diagnosing NIFTP.[87,162]

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.[163] 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.[164] FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.[45,114] Therefore, the tumor is often simply referred to as a "follicular neoplasm" by the cytopathologist (see *Nodule Evaluation* in the NCCN Guidelines for Thyroid Carcinoma).[81] The diagnosis of follicular thyroid carcinoma is assigned only after analysis of the permanent histologic sections—obtained from diagnostic lobectomy or thyroidectomy—shows tumor capsule invasion by follicular cells.

Highly invasive follicular thyroid carcinomas are much less common; they are sometimes recognized at surgery by their invasion of surrounding tissues and extensive invasion of blood vessels. Up to 80%

of these cancers metastasize, causing death in about 20% of patients, often within a few years of diagnosis.[129] The poor prognosis is closely related to older age at the time of diagnosis, advanced tumor stage, and larger tumor size.[12] The mortality rates for papillary and follicular thyroid carcinomas are similar in patients of comparable age and disease stage. Patients with either cancer have an excellent prognosis if the tumors are confined to the thyroid, are small, and are minimally invasive. However, patients with either papillary or follicular thyroid carcinoma have far less favorable outcomes if their disease is highly invasive or they develop distant metastases.[12,165]

When Hürthle (oncocytic) cells constitute most (or all) of the mass of a malignant tumor, the disease is often classified as Hürthle cell carcinoma, although the WHO classification and the AJCC consider it as a variant of follicular thyroid carcinoma.[9,166] Molecular studies suggest, however, that this tumor may be more similar to papillary than to follicular thyroid carcinomas.[167,168] 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.[169] 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.[170,171] 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.[172-174] In contrast to papillary or follicular carcinomas, 131I may be not effective in patients with Hürthle cell carcinoma because fewer Hürthle cell carcinomas concentrate 131I. In a series of 100 patients with distant metastases, 131I uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell carcinomas.[172] In the National Cancer Data Base report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.[10]

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.[175] 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.[176,177] 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,[178] which may be the presenting feature and also may be associated with distant metastases.[175] Otherwise, small (<1.5 cm) papillary or follicular carcinomas confined to the thyroid almost never cause distant metastases. Furthermore, recurrence rates after 30 years are one third of those associated with larger tumors; the 30-year cancer-specific mortality is 0.4% compared to 7% ($P < .001$) for tumors 1.5 cm or larger.[12] In fact, the prognosis for papillary and follicular thyroid carcinomas is incrementally poorer as tumors increase in size.[165,179] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas.[12]

Local Tumor Invasion

Up to 10% of differentiated thyroid carcinomas invade through the outer border of the gland and grow directly into surrounding tissues, increasing both morbidity and mortality. The local invasion may be microscopic or gross; it can occur with both papillary and follicular carcinomas.[12,180] Recurrence rates are 2 times higher with locally invasive tumors, and as many as 33% of patients with such tumors die of cancer within a decade.[12,181]

Lymph Node Metastases

In one review, nodal metastases were found in 36% of 8029 adults with papillary carcinoma, in 17% of 1540 patients with follicular thyroid carcinoma, and in up to 80% of children with papillary carcinoma.[129] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[182] The prognostic importance of regional lymph node metastases is controversial.[3] However, an analysis of more than 9900 patients in the SEER database found a significant difference in survival at 14 years for those with and without lymph node metastases (79% vs. 82%, respectively).[183] Older patients (>45 years) with papillary carcinoma and lymph node metastases also have decreased survival.[184] A 2012 review by Randolph et al emphasized the correlation between the size and number of metastatic lymph nodes and the risk of recurrence.[185] Identification of fewer than 5 sub-cm metastatic lymph nodes was associated with a low risk of recurrence. Conversely, structural disease recurrence rates of more than 20% to 30% were seen in large-volume lymph node metastases (>3 cm, or >5–10 involved lymph nodes).

Distant Metastases

Distant metastases are the principal cause of death from papillary and follicular carcinomas.[186,187] About 50% of these metastases are present at the time of diagnosis.[129] Distant metastases occur even more often in patients with Hürthle cell carcinoma (35%) and in those patients who are older than age 40 years at diagnosis.[172,173] Among 1231 patients in 13 studies, the sites of reported distant metastases were lung (49%), bone (25%), both lung and bone (15%), and the central nervous system (CNS) or other soft tissues (10%). The main predictors of outcome for patients with distant metastases are patient's age, the site of the distant metastasis, and whether the metastases concentrate 131I.[172,173,188,189]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[129] Even so, some pulmonary metastases are compatible with long-term survival.[190] For example, one study found that when distant metastases were confined to the lung, more than 50% of the patients were alive and free of disease at 10 years, whereas no patients with skeletal metastases survived that long.[191] The survival rates are highest in young patients with diffuse lung metastases seen only on 131I imaging and not on x-ray.[189,191,192] Prognosis is worse with large pulmonary metastases that do not concentrate 131I.[172,173,188]

Tumor Staging

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

Discussion) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[194] and not the 6th or 7th editions.[9,193]

Prognostic Scoring Strategies

Several staging and clinical prognostic scoring strategies use patient age older than 40 years as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma.[9,127,133,193,195] These strategies include the EORTC, TNM 7th edition, AMES (Age, Metastases, Extent, and Size), and AGES (Age, tumor Grade, Extent, and Size). All of these strategies effectively distinguish between patients at low and high risk.[179] With incrementally worsening MACIS (Metastasis, Age, Completeness of resection, Invasion, and Size) scores of less than 6, 6 to 6.99, 7 to 7.99, and 8+, however, the 20-year survival rates were 99%, 89%, 56%, and 24%, respectively.[133]

Unfortunately, a study that classified 269 patients with papillary carcinoma according to 5 different prognostic paradigms found that some patients in the lowest-risk group from each approach died of cancer.[136] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[193,196] The AJCC TNM staging approach (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 45 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,[197,198] TNM staging was not established as a predictor of recurrence and therefore does not accurately forecast the recurrences that often occur in patients who developed thyroid carcinoma when they were young. Two studies have shown the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.[127,199]

A three-tiered staging system—low, intermediate, high—that uses clinicopathologic features to risk stratify with regard to the risk of recurrence has been suggested and validated.[3,200-203] This staging system effectively risk stratifies patients with regard to the risk of recurrence, risk of persistent disease after initial therapy, risk of having persistent structural disease, likelihood of achieving remission in response to initial therapy, and likelihood of being in remission at final follow-up. In another approach, emphasis has been placed on evaluation of response to therapy using a dynamic risk assessment approach in which the initial risk estimates are modified during follow-up as additional data are accumulated.[204] This allows ongoing re-assessment of risk and allows the management paradigm to be better tailored to realistic estimates of risk that may change substantially over time.

Surgical Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total Thyroidectomy

The appropriate extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk papillary carcinoma, which is reflected in the NCCN category 2B recommendations for these procedures (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma and *Papillary Thyroid Carcinoma* in this Discussion). In most clinical settings, decisions about the extent of thyroidectomy should be individualized and done in consultation with the patient.[205] Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring[135] and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic Cancer Center for low-risk PTCs (MACIS score ≤3.99) had no improvement in survival rates after undergoing procedures more extensive than ipsilateral lobectomy. Thus, the authors concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[206]

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

Most NCCN Panel Members recommend total thyroidectomy for patients with biopsy-proven papillary carcinoma who have large-volume pathologic N1 metastases (>5 involved nodes with metastases >2 mm in largest dimension),[3,34,208] because this procedure is associated with improved disease-free survival.[121,137,207,209] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.[129,206] After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and 131I therapy)[12] and the highest frequency (11%) of subsequent pulmonary metastases.[210] However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.[41] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.[12]

However, some prominent thyroid cancer specialists (including some at NCCN Member Institutions) oppose this view and advocate unilateral lobectomy for most patients with papillary and follicular carcinoma based on 1) the low mortality among most patients (ie, those patients categorized as low risk by the AMES and other prognostic classification schemes); and 2) the high complication rates reported with more extensive thyroidectomy.[134,195,211] The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole-body 131I imaging. Panel members recommend total lobectomy (without radioactive iodine RAI ablation) for patients with papillary carcinoma who have small-volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm, in largest dimension).[212]

NCCN Panel Members believe that total lobectomy alone is adequate treatment for papillary microcarcinomas provided the patient has not been exposed to radiation, has no other risk factors, and has a tumor smaller than 1 cm that is unifocal and confined to the thyroid without vascular invasion (see *Primary Treatment* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,12,175,213-216] Total lobectomy alone is also adequate treatment for NIFTP pathologies (see *Tumor Variables Affecting Prognosis, Histology*) and minimally invasive follicular thyroid carcinomas (see *Primary Treatment* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). However, completion thyroidectomy is recommended for any of the following: tumor more than 4 cm in diameter, positive resection margins, gross extrathyroidal extension, macroscopic multifocal disease, macroscopic nodal metastases, confirmed contralateral disease, or vascular invasion.[3] Note that "gross extrathyroidal extension" refers to spread of the primary tumor outside of the thyroid capsule with invasion into the surrounding structures such as strap muscles, trachea, larynx, vasculature, esophagus, and/or recurrent laryngeal nerve.[149,217,218]

Completion Thyroidectomy

This procedure is recommended when remnant ablation is anticipated or if long-term follow-up is planned with serum Tg determinations and with (or without) whole-body 131I imaging. Large thyroid remnants are difficult to ablate with 131I.[210] Completion thyroidectomy has a complication rate similar to that of total thyroidectomy. Some experts recommend completion thyroidectomy for routine treatment of tumors 1 cm or larger, because approximately 50% of patients with cancers this size have additional cancer in the contralateral thyroid lobe.[180,219-225] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[222]

Miccoli et al studied irradiated children from Chernobyl who developed thyroid carcinoma and were treated by lobectomy; they found that 61% had unrecognized lung or lymph node metastases that could only be identified after completion thyroidectomy.[137] In another study, patients who underwent completion thyroidectomy within 6 months of their primary operation developed significantly fewer lymph node and hematogenous recurrences, and they survived significantly longer than did those in whom the second operation was delayed for more than 6 months.[223]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy.[205] Transient clinical hypoparathyroidism after surgery is common in adults[226] and children[137,227] undergoing total thyroidectomy. The rates of long-term recurrent laryngeal nerve injury and hypoparathyroidism, respectively, were 3% and 2.6% after total thyroidectomy and 1.9% and 0.2% after subtotal thyroidectomy.[228] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[229] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[230] When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5860 patients found that surgeons who performed more than 100 thyroidectomies a year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies a year had 4 times as many complications.[231]

Radioactive Iodine Therapy

Postoperative Radioactive Iodine (RAI)

The NCCN Panel recommends a selective use approach to postoperative RAI administration. The 3 general, but overlapping, functions of postoperative RAI administration include: 1) ablation of the normal thyroid remnant, which may help in surveillance for recurrent disease (see below); 2) adjuvant therapy to try to eliminate suspected micrometastases; or 3) RAI therapy to treat known persistent disease. The NCCN Guidelines have 3 different pathways for postoperative RAI administration based on clinicopathologic factors: 1) RAI typically recommended; 2) RAI selectively recommended; and 3) RAI not typically recommended (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma). Postoperative RAI is typically recommended for patients at high risk of having persistent disease remaining after total thyroidectomy and includes patients with any of the following factors: 1) gross extrathyroidal extension; 2) a primary tumor greater than 4 cm; or 3) postoperative unstimulated Tg greater than 5 to 10 ng/mL (see *Clinicopathologic Factors* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).

Postoperative RAI is recommended or considered for patients with known/suspected distant metastases at presentation. Postoperative RAI is also recommended for select patients who are at greater risk for recurrence with any of the following clinical indications such as primary tumor 2 to 4 cm, high-risk histology, lymphatic invasion, cervical lymph node metastases, macroscopic multifocality (one focus >1 cm), or unstimulated postoperative serum Tg (<5–10 ng/mL).[3,232,233] However, the NCCN Panel does not routinely recommend RAI for patients with all of the following factors: 1) either unifocal or multifocal classic papillary microcarcinomas (<1 cm) confined to the thyroid; 2) no detectable anti-Tg antibodies; and 3) postoperative unstimulated Tg less than 1 ng/mL. Guidelines from the ATA list very similar indications for postoperative RAI use and also provide specific guidance regarding the safe use of RAI in the outpatient setting.[3,234]

Studies show decreased recurrence and disease-specific mortality for populations at intermediate or higher risk when postoperative 131I therapy is administered as part of the initial treatment.[12,128,136,235-237] In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was about 3-fold higher in patients either treated with thyroid hormone alone or given no postoperative medical therapy when compared with patients who underwent postoperative thyroid remnant ablation with 131I ($P < .001$). Moreover, fewer patients developed distant metastases ($P < .002$) after thyroid remnant 131I ablation than after other forms of postoperative treatment. However, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter.[235] Another study of 21,870 intermediate risk patients with differentiated thyroid cancer found that postoperative RAI improved OS ($P < .001$) and was associated with a 29% reduction in the risk of death after adjustment for demographic and clinical factors (hazard risk, 0.71; 95% CI, .62–.82; $P < .001$).[237] Some studies have found that remnant ablation had less of a therapeutic effect, perhaps because more extensive locoregional surgery had been done.[179]

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.[238] Longer follow-up suggests that overall survival is not decreased or increased in these patients.[239] However, a more recent study reported that the incidence of secondary malignancies, such as leukemia and salivary gland malignancies, has increased in patients with low-risk thyroid cancer (ie, T1N0) who received RAI.[240] Debate continues about ablating the thyroid bed with 131I after total thyroidectomy.[3,179,235,241] In patients with papillary carcinoma who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates.[216,233,242] A long-term study (n=1298) found that overall survival is not improved in patients who receive RAI ablation.[243] Reasons favoring remnant ablation include: 1) simplified patient follow-up, because elimination of thyroid bed uptake prevents misinterpretation of it as disease; 2) elimination of normal tissue as a source of Tg production, which facilitates identification of patients who are free of disease and may simplify their care while promoting early identification of those with residual cancer; and 3) elimination of normal tissue, which may eliminate the nidus for continued confounding anti-Tg antibody production. Conversely, others argue that most recurrences can be easily detected with neck ultrasound and that serum Tg levels are often quite low after a total thyroidectomy. Therefore, in patients at low and intermediate risk, the clinical benefit of routine remnant ablation as a requirement for optimal follow-up remains uncertain.

Data suggest that lower doses of RAI are as effective as higher doses—30 versus 100 mCi—for ablation in patients with low-risk thyroid cancer (eg, T1b/T2 [1–4 cm], clinical N0 disease).[32,33] The NCCN Guidelines reflect a more cautious approach to using RAI ablation based on these randomized trials.[244] If RAI ablation is used, the NCCN Guidelines recommend (category 1) 30 mCi of 131I for RAI ablation in patients at low risk based on these randomized trials. This same ablation dose—30 mCi—may be considered (category 2B) in patients at slightly higher risk (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Papillary, Follicular, and Hürthle Cell Carcinoma).[245] RAI ablation is not recommended in patients at very low risk.

RAI therapy for thyroid cancer carries the risk of possible adverse effects including salivary gland dysfunction, lacrimal gland dysfunction, transient gonadal dysfunction, and secondary primary malignancies.[246] The possible benefits of RAI should be weighed with the risk of adverse effects as part of treatment decision making.[244] Adverse effects may be minimized by using lower doses of RAI.[32]

Diagnostic Total Body Imaging and Thyroid Stunning

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

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

Postoperative Administration of RAI

Historically, the 3 methods of determining 131I therapy activities (doses) have included: empiric fixed doses, quantitative dosimetry, and upper-bound limits that are set by blood dosimetry.[3,247,250,256,257] Most patients at NCCN Member Institutions receive postoperative RAI based on empiric fixed dosing; a few centers use a combination of blood dosimetry and quantitative lesional dosimetry. In the past, hospitalization was required to administer therapeutic doses of 131I greater than 30 mCi (1110 MBq). However, hospitalization is no longer necessary in most states, because a change in federal regulations permits the use of much larger 131I doses in patients who are ambulatory.[256] However, 131I therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses.

Administration of a fixed dose of 131I is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of 131I in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of 131I. Lymph node metastases may be treated with about 100 to 175 mCi (3700–6475 MBq) of 131I. Cancer growing through the thyroid capsule (and incompletely resected) is treated with 150 to 200 mCi (5550–7400 MBq). Patients with distant metastases are usually treated with 100 to 200 mCi (3700–7400 MBq) of 131I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in the elderly and in those with impaired kidney function.[258,259] Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of 131I (which is very uncommon) are treated with 150 mCi of 131I (5550 MBq) or less to avoid lung injury, which may occur when more than 80 mCi remains in the whole body 48 hours after treatment. The administered activity of RAI therapy should be adjusted for pediatric patients.[3,260-262] A pilot study demonstrated that targeted therapy of the MAP kinase pathway with a MEK inhibitor (selumetinib) significantly increased the effectiveness of RAI therapy in patients who were previously RAI refractory.[263]

Post-Treatment 131I Imaging

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

Assessment and Management After Initial Treatment

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

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

Recombinant Human TSH

During follow-up, periodic withdrawal of thyroid hormone therapy has traditionally been used to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements with (or without) 131I imaging could be performed to detect residual thyroid tissue or carcinoma. However, patients dislike thyroid hormone withdrawal, because it causes symptomatic hypothyroidism. An alternative to thyroid hormone withdrawal is the administration of rhTSH intramuscularly, which stimulates thyroidal 131I uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.[269] Administration of rhTSH is well tolerated; nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[267] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[269]

An international study was performed to assess the effects of 2 rhTSH dosing schedules on whole-body 131I imaging and serum Tg levels when compared with imaging and Tg levels obtained after thyroid hormone withdrawal.[267] Data showed that the combination of rhTSH–stimulated whole-body imaging and serum Tg measurements detected 100% of metastatic carcinoma.[267] In this study, 0.9 mg of rhTSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of 131I on the third day. Whole-body imaging and Tg measurements were performed on the fifth day. Whole-body 131I images were acquired after 30 minutes of imaging or after obtaining 140,000 counts, whichever came first. A serum Tg of 2.0 ng/mL or higher, obtained 72 hours after the last rhTSH injection, indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole-body imaging findings.[267,270]

Measuring Serum Tg and Anti-Tg Antibodies

Serum Tg measurement is the best means of detecting thyroid tissue, including carcinoma. Tg can be measured when TSH has been stimulated—either by thyroid hormone withdrawal or by rhTSH—because in this setting, serum Tg has a lower false-negative rate than whole-body 131I imaging.[266-268,271] Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or rhTSH stimulation. Serum Tg generally does not increase as much after rhTSH administration as after withdrawal of thyroid hormone. The conditions for rhTSH–stimulated, whole-body 131I imaging stipulate using 4-mCi 131I doses (based on the trial)[267] 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]).[272,273] 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).[274,275] 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.[272,275,276] 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.[276]

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.[277] In patients with coexistent autoimmune thyroid disease at the time of surgery, anti-Tg antibodies may persist far longer. In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for up to 20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.[278] Patients with persistently undetectable serum Tg and anti-Tg antibody levels have longer disease-free survival when compared with patients who have detectable levels.[279]

Treating Patients With Positive Tg and Negative Imaging

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

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

Thyroid Hormone Suppression of TSH

The use of postoperative levothyroxine to decrease TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma, because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium.[3,250,283,284] However, the optimal serum levels of TSH have not been defined because of a lack of specific data; therefore, the NCCN Panel recommends tailoring the degree of TSH suppression to the risk of recurrence and death from thyroid cancer for each individual patient. For patients with known residual carcinoma or those at high risk for recurrence, the recommended TSH level is below 0.1 milliunits/L. For patients at low risk and for those patients with an excellent response to initial therapy who are in remission, the recommended TSH level is either slightly below or slightly above the lower limit of the reference range. The risk and benefit of TSH-suppressive therapy must be balanced for each individual patient because of the potential toxicities associated with TSH-suppressive doses of levothyroxine, including cardiac tachyarrhythmias (especially in the elderly), bone demineralization (particularly in post-menopausal women), and frank symptoms of thyrotoxicosis.[3,285] An adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d) is recommended for patients whose TSH levels are chronically suppressed. However, reports do not suggest that bone mineral density is altered in patients receiving levothyroxine.[286,287]

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated with thyroid hormone suppressive therapy.[12,235,238,284,288-290] The average dosage needed to attain serum TSH levels in the euthyroid range is higher in patients who have been treated for thyroid carcinoma (2.11 mcg/kg per day) than in those patients with spontaneously occurring primary hypothyroidism (1.62 mcg/kg per day).[290] Even higher doses are required to suppress serum TSH in patients who have been treated for thyroid carcinoma. The optimal TSH level to be achieved is uncertain in patients who have been treated for thyroid carcinoma. Superior outcomes were associated with aggressive thyroid hormone suppression therapy in patients at high risk but were achieved with modest suppression in patients with stage II disease.[238] Excessive TSH suppression (into the undetectable, thyrotoxic range) is not required to prevent disease progression in all patients who have been treated for differentiated thyroid carcinoma.

Adjuvant External-Beam RT

No prospective controlled trials have been completed using adjuvant external-beam radiation therapy (EBRT).[291-293] One retrospective study reported a benefit of adjuvant EBRT after RAI in patients older than 40 years of age with invasive papillary carcinoma (T4) and lymph node involvement (N1).[294] Local recurrence and locoregional and distant failure were significantly decreased. A second study reported increased cause-specific survival and local relapse-free rate in select patients treated with adjuvant EBRT (in addition to total thyroidectomy and TSH-suppressive therapy with thyroid hormone) for papillary carcinoma with microscopic residuum. Not all patients received RAI therapy.[128] 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%).[295]

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%).[295] However, these patients had not received RAI. Similar benefit was shown with RAI alone in comparable patients treated with RAI after surgery.[295] 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.[296] Other data from single institutions also show that adjuvant EBRT yields long-term control of locoregional disease.[297-299] Studies suggest that intensity-modulated radiation therapy (IMRT) is safe, effective, and less morbid in patients with thyroid cancer.[297,300]

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.[301,302] Brain metastases pose a special problem, because 131I therapy may induce cerebral edema. Neurosurgical resection can be considered for brain metastases. For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery is preferred over whole brain radiation.[303,304] 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.[305] Most recurrent tumors respond well to surgery; 131I therapy; EBRT, SBRT, or IMRT; or other local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA).[3,306]

Systemic Therapy

Systemic therapy can be considered for tumors that are not surgically resectable; are not responsive to 131I; are not amenable to EBRT treatment, SBRT, IMRT, or other local therapies; and have clinically significant structural disease progression during the last 6 to 12 months. Among 49 patients with metastatic differentiated thyroid carcinoma who were treated with 5 chemotherapy protocols, only 2 (3%) patients had objective responses.[307] In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.[308] Combination chemotherapy is not clearly superior to doxorubicin therapy alone.[129] Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease.[309] Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.[310-317] Agents include multitargeted kinase inhibitors, such as lenvatinib,[310,313,318-324] sorafenib,[325-332] sunitinib,[330,333] axitinib,[334-336] everolimus,[337] vandetanib,[338] cabozantinib,[311,339] and pazopanib;[340] and BRAF V600E mutation inhibitors, such as vemurafenib and dabrafenib.[341-344] Data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in patients with papillary carcinoma who have ALK gene fusion.[345-348]

Clinical trials suggest that kinase inhibitors have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of subjects, usually for about 12 to 24 months.[313,321,330,340,349-351] 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).[320,325] 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).[352-355] Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, stroke, and liver toxicity; however, most side effects can be managed and are reversible with discontinuation of the drug.[320,321,356-361] Dose modifications of kinase inhibitors may be required. Pazopanib has been reported to cause reversible hypopigmentation.[362]

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.[363] 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.[364] Surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients.[365] In more than 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 33% of subjects.[366] Preoperative ultrasound findings altered the operation in more than 40% of cases. In another report,[367] operative management was altered in 23% of the total group due to findings on the preoperative ultrasound. These studies indicate that preoperative ultrasound has a high sensitivity for nodal disease and will detect nonpalpable nodal metastases in 20% to 33% of patients, and ultrasound should alter the index operation in a similar percentage of patients. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases. Cross-sectional imaging (CT or MRI) should be performed if the thyroid lesion is fixed, bulky, or substernal. Iodinated contrast is required for optimal cervical imaging with CT, although iodinated contrast will delay treatment with RAI. Evaluation of vocal cord mobility may be considered for patients with abnormal voice, a surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Vocal cord mobility may be evaluated by ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy.[368]

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

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

A study of more than 5000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for patients at low and high risk.[373] An observational study (SEER database) in more than 35,000 patients with PTC limited to the thyroid gland suggests that survival is similar whether (or not) patients are treated in the first year after diagnosis and whether they undergo lobectomy or total thyroidectomy.[374] However, most guidelines (eg, NCCN, ATA) do not recommend active surveillance for patients with PTC.[3] Another study of 2784 patients with differentiated thyroid carcinoma (86% with PTC) found that total thyroidectomy was associated with increased survival in patients at high risk.[238] A study in 52,173 patients found that total thyroidectomy reduces recurrence rates and improves survival in patients with PTC of 1 cm or more when compared with lobectomy.[375] For patients at lower risk who undergo lobectomy plus isthmusectomy, completion of thyroidectomy is recommended for any one of the following risk factors: large tumor (>4 cm), positive resection margins, gross extrathyroidal extension, macroscopic multifocal disease, vascular invasion, or macroscopic nodal metastases. While a retrospective study using the National Cancer Database has shown that a sizable percentage of patients with differentiated thyroid cancer receive RAI therapy following lobectomy[376], the panel does not support this practice due to a lack of data showing benefit. Therefore, RAI is not recommended following lobectomy for differentiated thyroid cancer.

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

Radioactive Iodine Therapy

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

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

For patients with unresectable gross residual disease in the neck (suspected or proven) that is refractory to RAI, EBRT or IMRT can be considered if disease is threatening vital structures (see *Postsurgical Evaluation* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3,297,298,377-379]

Surveillance and Maintenance

The recommendations for surveillance and maintenance are described in the algorithm (see *Surveillance and Maintenance* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3] About 85% of patients are considered to be low risk after surgery for papillary thyroid cancer.[3] In patients who have had total (or near total) thyroidectomy and thyroid remnant ablation, the ATA Guidelines define the absence of persistent tumor (also known as no evidence of disease [NED]) as: 1) absence of clinical evidence of tumor; 2) absence of imaging evidence of tumor; and 3) undetectable Tg levels (during either TSH suppression or TSH stimulation) and absence of anti-Tg antibodies.[3] Patients treated with 131I ablation may be followed with unstimulated Tg annually and with periodic neck ultrasound if they have negative ultrasounds, stimulated Tg less than 2 ng/mL (with negative anti-Tg antibodies), and negative RAI imaging (if performed). However, if they have a clinical suggestion of recurrent disease, then TSH-stimulated testing (or other imaging) may be considered. A subgroup of patients at low risk (eg, micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic neck ultrasound follow-up (without stimulated Tg or follow-up whole-body imaging) as long as their basal Tg remains low (see *Surveillance and Maintenance* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.[3] Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.[3]

RAI imaging (TSH-stimulated [during either TSH suppression or TSH stimulation]) can be considered in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality; patients with previous RAI-avid metastases; or patients with abnormal Tg levels, stable or increasing anti-Tg antibodies, or abnormal ultrasound results. In patients selected for monitoring with RAI imaging it is recommended every 12 to 24 months until no clinically significant response is seen to RAI treatment in patients with iodine-responsive tumors and detectable Tg, distant metastases, or soft tissue invasion on initial staging. Non-RAI imaging—such as ultrasound of the central and lateral neck compartments, neck CT, chest CT, or FDG-PET/CT—may be considered if RAI imaging is negative and stimulated Tg is greater than 2 to 5 ng/mL. High-risk factors include incomplete tumor resection, macroscopic tumor invasion, and distant metastases in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality (see *Consideration for Initial Postoperative RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).[3]

Recurrent Disease

The NCCN Panel agrees that surgery is the preferred therapy for locoregional recurrent disease if the tumor is resectable (see *Recurrent Disease* in the NCCN Papillary [Thyroid] Carcinoma algorithm). Cervical ultrasound, including the central and lateral compartments, is the principal imaging modality when locoregional recurrence is suspected.[3] Cross-sectional imaging with CT or MRI may also be valuable for evaluation and surgical planning, especially when reliable high-resolution diagnostic ultrasound is unavailable and/or there is suspicion of invasion into the aerodigestive tract. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases.

Clinically significant nodal recurrence in a previously undissected nodal basin should be treated with a formal compartmental resection.[3] In the central neck, this is usually achieved through a unilateral level VI dissection and, occasionally, a level VII dissection. In the lateral compartment, a formal modified radical neck dissection—including levels II, III, IV, and Vb—should be performed. Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Selective dissection of individual nodal metastases (cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field, and is not recommended in the NCCN Guidelines for Thyroid Carcinoma. Clinically significant nodal recurrence detected in a previously dissected nodal basin may be treated with a more focused dissection of the region containing the metastatic disease. For example, a level II recurrence detected in a patient who underwent a modified radical neck dissection as part of the primary treatment may only require selective dissection of level II. Likewise, a central neck recurrence detected in a patient who underwent a central neck dissection as part of the primary treatment may only require a focused resection of the region of recurrence.

For unresectable locoregional recurrence, RAI treatment and EBRT or IMRT are recommended if the 131I imaging is positive.[296,372] Local therapies, such as ethanol ablation or RFA, are also an option if available. EBRT or IMRT alone is another option in the absence of 131I uptake for select patients not responsive to other therapies.[298,380 300,382] [300,382] When recurrent disease is suspected based on high serum-stimulated Tg values (>10 ng/mL) and negative imaging studies (including PET scans), RAI therapy can be considered using an empiric fixed dose of 100 to 150 mCi of 131I (see *Recurrent Disease* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). The NCCN Panel had a major disagreement about recommending (category 3) post-treatment 131I imaging in this setting, because some do not feel that these patients should have imaging. No study has shown a decrease in morbidity or mortality in patients treated with 131I on the basis of increased Tg measurements alone. In a long-term follow-up study, no survival advantage was associated with empiric high-dose RAI in patients with negative imaging.[381] 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.[382,383] Observation may be considered for patients with low-volume disease that is stable and distant from critical structures.

Metastatic Disease Not Amenable to RAI Therapy

For metastatic disease not amenable to RAI therapy, several therapeutic approaches are recommended, depending on the site and number of tumor foci (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary

[Thyroid] Carcinoma).[3,384] 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.[301,302,385-387] 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.[388-390] Embolization (or other interventional procedures) of metastases can also be considered either prior to resection or as an alternative to resection.[385,391]

For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred (see the NCCN Guidelines for Central Nervous System Cancers).[303,304] For multiple CNS lesions, surgical resection and/or EBRT can be considered (see *Treatment of Metastatic Disease Not Amenable to RAI Therapy* in the NCCN Guidelines for Papillary [Thyroid] Carcinoma).

For clinically progressive or symptomatic disease, recommended options include: 1) lenvatinib (preferred) or sorafenib;[320,325] 2) clinical trials for non-131I–responsive tumors; 3) consider other non-FDA approved small molecule kinase inhibitors or systemic therapy if a clinical trial is not available; or 4) consider resection of distant metastases and/or EBRT or IMRT.[392,393] The recommendations for lenvatinib (preferred) or sorafenib are based on phase 3 randomized trials.[320,325] The NCCN Panel feels that lenvatinib is the preferred agent in this setting based on a response rate of 65% for lenvatinib when compared with 12% for sorafenib, although these agents have not been directly compared.[318,320,325] The decision to use lenvatinib or sorafenib should be individualized for each patient based on likelihood of response and comorbidities. The efficacy of lenvatinib or sorafenib for patients with brain metastases has not been established; therefore, consultation with neurosurgeons and radiation oncologists is recommended. Kinase inhibitors have been used as second-line therapy for thyroid cancer.[321,322]

Lenvatinib was compared with placebo in patients with metastatic differentiated thyroid cancer that was refractory to RAI in a phase 3 randomized trial.[320] Patients receiving lenvatinib had a progression-free survival (PFS) of 18.3 months compared with 3.6 months for those receiving placebo (hazard ratio [HR], 0.21; 99% CI, 0.14–0.31; $P < .001$). Six treatment-related deaths occurred in the lenvatinib group.

Another phase 3 randomized trial compared sorafenib with placebo in patients with RAI-refractory metastatic differentiated thyroid cancer.[325] Patients receiving sorafenib had a PFS of 10.8 months compared with 5.8 months for those receiving placebo (HR, 0.59; 95% CI, 0.45–0.76; $P < .0001$). One treatment-related death occurred in the sorafenib group. Hand-foot syndrome is common with sorafenib and may require dose adjustments.

Other commercially available small-molecule kinase inhibitors may also be considered for progressive and/or symptomatic disease—including axitinib, everolimus, pazopanib, sunitinib, vandetanib, cabozantinib, or vemurafenib (for BRAF-positive disease)—although none have been approved by the FDA for differentiated thyroid cancer (see *Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma* in the NCCN Guidelines for Thyroid Carcinoma).[392] Note that kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.[320,325,357,394,395] Active surveillance is often appropriate for asymptomatic patients with indolent disease and no brain metastasis.[321,357]

Because chemotherapy is usually not effective for non-RAI avid tumors, the NCCN Guidelines recommend clinical trials for treatment of these tumors; small molecule kinase inhibitors (ie, axitinib, sunitinib, pazopanib, vandetanib) or traditional cytotoxic systemic therapy can be considered if a trial is not available.[3,326,328,331,332,334,340,357,396,397] However, kinase inhibitor therapy may be most appropriate for patients with unresectable recurrent disease that is threatening vital structures or is not responsive to EBRT or IMRT.[398] Of interest, hypothyroidism has been reported in some patients receiving sunitinib or sorafenib, but it also seems to be associated with increased PFS.[359,395]

Follicular Thyroid Carcinoma

The diagnosis and treatment of papillary and follicular thyroid carcinoma are similar; therefore, only the important differences in the management of follicular carcinoma are highlighted. The diagnosis of follicular thyroid carcinoma requires evidence of invasion through the capsule of the nodule or the presence of vascular invasion.[45,399] Unlike PTC, FNA is not specific for follicular thyroid carcinoma and accounts for the main differences in management of the 2 tumor types.[74,81,114,400] 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.[399,401] 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.[402] Minimally invasive cancers, as well as NIFTP tumors, may also be simply followed carefully, because minimally invasive follicular carcinomas and NIFTP usually have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma do occasionally occur. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see *Recurrent Disease* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

The other features of management and follow-up for follicular thyroid carcinoma are similar to those of PTC. Clinicopathologic factors can be used to guide decisions about whether to administer initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 2 to 4 cm, but the final decision depends on the combination of individual clinical factors as outlined in the algorithm. The NCCN Guidelines provide algorithms to assist in decision making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Follicular [Thyroid] Carcinoma).

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

Hürthle Cell Carcinoma

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

The management of Hürthle cell carcinoma is almost identical to follicular thyroid carcinoma, except that 1) locoregional nodal metastases may be more common, and therefore therapeutic lymph node dissections of the affected compartment may be needed for clinically apparent biopsy-proven disease; and 2) metastatic Hürthle cell tumors are less likely to concentrate 131I (see *Papillary Thyroid Cancer*: *Surgical Therapy* in this Discussion).[406] Postoperative EBRT or IMRT can be considered for: 1) unresectable primary Hürthle cell lesions that do not concentrate 131I if disease is threatening vital structures; and 2) unresectable locoregional recurrence (see *Postsurgical Evaluation* and *Recurrent Disease* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma), similar to the management for follicular thyroid carcinoma.[3]

Clinicopathologic factors can be used to guide decisions about whether to use initial postoperative RAI (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). For example, RAI may be recommended when the primary tumor is 2 to 4 cm, but the final decision about whether to use RAI depends on the combination of individual clinical factors as outlined in the algorithm. The NCCN Guidelines provide algorithms to assist in decision making about use of RAI in different settings: 1) RAI is not typically indicated for patients classified as having a low risk of recurrence/disease-specific mortality; 2) RAI may be considered for patients without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and 3) RAI is often used for patients with known or suspected distant metastatic disease (see *Clinicopathologic Factors* in the NCCN Guidelines for Hürthle cell [Thyroid] Carcinoma).

RAI therapy has been reported to decrease the risk of locoregional recurrence and is recommended for unresectable disease with positive 131I imaging. 131I therapy (100–150 mCi) may be considered after thyroidectomy for patients with stimulated Tg levels of more than 10 ng/mL who have negative scans (including FDG-PET) (see *Recurrent Disease* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma).[171] Pretreatment diagnostic imaging (123I or low-dose 131I) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) may be considered based on pathology, postoperative Tg, and intraoperative findings (see *RAI Being Considered Based on Clinicopathologic Features* in the NCCN Guidelines for Hürthle Cell [Thyroid] Carcinoma). However, some NCCN Panel Members did not feel that diagnostic total body imaging should be recommended before 131I therapy is administered, because the thyroid remnant may interfere with the scan, making this a category 2B recommendation.[3]

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid.[407-410] Sporadic MTC accounts for about 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as: 1) MEN type 2A (MEN 2A), which is the most common type; and 2) MEN 2B.[411,412] Familial MTC is now viewed as a variant of MEN 2A.[407,408,413] Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of the disease tend to present at earlier ages.[407,408] The 5-year relative survival for stages I to III is about 93%, whereas 5-year survival for stage IV is about 28%.[9,10] 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.[414] Distant metastases in the lungs or bones cause symptoms in 5% to 10% of patients. Many patients with advanced MTC can have diarrhea, Cushing's syndrome, or facial flushing, because the tumor can secrete calcitonin and sometimes other hormonally active peptides (ie, adrenocorticotropic hormone [ACTH], calcitonin gene-related peptide [CGRP]). Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms.[415] 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.[416-418] However, routine measurement of the basal serum calcitonin concentration is not recommended by the NCCN Panel for evaluating a patient with nodular thyroid disease because of the expense of screening all thyroid nodules and only finding a few cases of MTC, the lack of confirmatory pentagastrin stimulation testing, and the resulting need for thyroidectomy in some patients who actually have benign thyroid disease.[419,420] The ATA is equivocal about routine calcitonin measurement.[3]

Inherited MTC

For patients in known kindreds with inherited MTC, prospective family screening with testing for mutant *RET* genes can identify disease carriers long before clinical symptoms or signs are noted.[409,410] 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[421] and because pentagastrin is no longer available in the United States. When MEN 2A is suspected, the NCCN Guidelines recommend measurement of calcium levels with (or without) serum intact parathyroid hormone levels (see *Additional Workup* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade of life, without gender preference. In patients with MEN 2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.

All familial forms of MTC and MEN 2 are inherited in an autosomal-dominant fashion. Mutations in the *RET* proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of familial MTC.[409,410,422] The *RET* proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN 2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; MEN 2B and some familial MTC mutations are found within the intracellular exons 14 to 16.[407,408] 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.[423,424] 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;[425] 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.[426]

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum carcinoembryonic antigen [CEA]) and screening of patients with germline *RET* proto-oncogene mutations for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A). Before surgery for MTC, it is important to diagnose and address coexisting pheochromocytoma to avoid hypertensive crisis during surgery (see *Pheochromocytoma/Paraganglioma* in the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org). Pheochromocytoma can be removed using laparoscopic adrenalectomy.[407,408,427] 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.[407,408] Liver imaging is rarely needed if the calcitonin is less than 400 pg/mL. Evaluation of vocal cord mobility can also be considered for patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.

Staging

As previously mentioned, the NCCN Guidelines for Thyroid Carcinoma do not use TNM stages to guide therapy. Instead, many characteristics of the tumor and patient play important roles in these NCCN Guidelines. Many specialists in thyroid cancer also follow this paradigm. The TNM criteria for clinicopathologic tumor staging are based on tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma) (7th edition of the AJCC Cancer Staging Manual).[9] Staging for MTC slightly changed in the 2010 AJCC update (ie, 7th edition of the AJCC Cancer Staging Manual).[9] In the 7th edition, T3, N0, M0 has been downstaged from stage III to stage II. All follow-up studies (in this Discussion) reporting on AJCC-TNM staging have referred to the 5th edition[194] and not to the 6th or 7th editions.[9,193] As previously mentioned, the 5-year relative survival for stages I to III MTC is about 93%, whereas 5-year survival for stage IV is about 28%.[9]

However, the TNM staging classification lacks other important prognostic factors.[428] 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.[414,428] Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically are diagnosed at an earlier age) is probably similar to those with sporadic disease.[429,430] Despite an even younger typical age at diagnosis, however, patients with MEN 2B who have MTC are more likely than those with MEN 2A (or familial MTC) to have locally aggressive disease.[430]

Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor;[431] 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level;[432] and 3) postoperative residual hypercalcitoninemia.[433] 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.[428,434] Codon analysis is useful for predicting prognosis.[407,408,435] Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease.[436] More than 95% of patients with MEN 2B have a mutation in exon 16 (codon 918), whereas 2% to 3% have a mutation in exon 15 (codon 883).[437]

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).[352-355] MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, 131I imaging cannot be used, and RAI treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, TSH suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levothyroxine dose.[407,408]

Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease, because the possibility of MEN 2 should dictate testing for a germline *RET* proto-oncogene mutation for all patients with MTC. Pheochromocytomas should be removed (eg, laparoscopic adrenalectomy) before surgery on the thyroid to avoid hypertensive crisis during surgery (see

Pheochromocytoma/Paraganglioma in the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org). Patients with pheochromocytomas must be treated preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery. Forced hydration and alpha-blockade are necessary to prevent hypotension after the tumor is removed. After institution of alpha-blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is 1 cm or larger or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is less than 1 cm and for unilateral thyroid disease (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).[369,414] 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.[407,408,438] Note that C634 mutations are the most common mutations.[407,408] Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN 2B who have codon 883 *RET* mutations, 918 *RET* mutations, or compound heterozygous (V804M + E805K, V804M + Y806C, or V804M + S904C) *RET* mutations (see *Clinical Presentation* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma), because these *RET* mutations carry the highest risk for MTC (ie, level D).[407,408,439]

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.[407,408,439,440] 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).[407,408,441,442] Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.[407,408,440,441,443] A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with RET mutations for MEN 2A; longer follow-up is necessary to determine if these patients are cured.[444]

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.[407,408] A bilateral central neck dissection (level VI) can be considered for all patients with MEN 2B. For those patients with MEN 2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if patients have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for these patients with primary tumor(s) 1 cm or larger in diameter (>0.5 cm for patients with MEN 2B) or for patients with central compartment lymph node metastases (see *Primary Treatment* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma).

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

Adjuvant RT

EBRT and IMRT have not been adequately studied as adjuvant therapy in MTC.[299,407,445] 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.[446] 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).[407,408] EBRT or IMRT can also be given to palliate painful or progressing bone metastases.[301,302,387,407,408]

Persistently Increased Calcitonin

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

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease, 15 patients with MEN 2A, and 6 patients with MEN 2B), the 5- and 10-year survival rates were 90% and 86%, respectively.[447] 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.[433,448] 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.[449] 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.[450,451] 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.[451]

Postoperative Management and Surveillance

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

Patients with detectable serum markers (ie, calcitonin levels ≥150 pg/mL) should have contrast-enhanced CT (±PET) or MRI of the neck, chest, and abdomen with a liver protocol. Bone scan and MRI of axial skeleton should be considered in select patients such as those with very elevated calcitonin levels.[407,408] The NCCN Panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but there is insufficient evidence to recommend any particular choice or combination of tests.[407,408]

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

Recurrent or Persistent Disease

Kinase inhibitors may be appropriate for select patients with recurrent or persistent MTC that is not resectable (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). Although kinase inhibitors may be recommended for patients with MTC, it is important to note that kinase inhibitors may not be appropriate for patients with stable or slowly progressive indolent disease.[321,452,453] Vandetanib and cabozantinib are oral receptor kinase inhibitors that increase PFS in patients with metastatic MTC.[353,355,454-456]

Vandetanib is a multitargeted kinase inhibitor; it inhibits RET, vascular endothelial growth factor receptor (VEGFR), and endothelial growth factor receptor (EGFR).[353] 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.[353] 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.[352] However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity.[457] 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).[353]

Cabozantinib is a multitargeted kinase inhibitor that inhibits RET, VEGFR2, and MET. In a phase 3 randomized trial (EXAM) in patients with locally advanced or metastatic MTC (n = 330), cabozantinib increased median PFS when compared with placebo (11.2 vs. 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; $P < .001$); overall survival data are not yet available.[355] In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC.[354,355,458,459] 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,[460] the following options can be considered: 1) EBRT or IMRT; 2) vandetanib (category 1); or 3) cabozantinib (category 1). Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include: 1) palliative resection, ablation (eg, radiofrequency, embolization), or other regional treatment; 2) vandetanib (category 1); or 3) cabozantinib (category 1) (see *Recurrent or Persistent Disease* in the NCCN Guidelines for Medullary [Thyroid] Carcinoma). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but active surveillance is acceptable given the lack of data regarding alteration in outcome. The NCCN Panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone.

In the setting of symptomatic disease or progression, the NCCN Panel recommends the following: 1) vandetanib (category 1);[353,456,461] 2) cabozantinib (category 1);[355] 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.[333,462-466] If the patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.[407,467-469] EBRT or IMRT can be used for local symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.[388-390] Best supportive care is also recommended.

Results from clinical trials have shown the effectiveness of novel multitargeted therapies including sunitinib,[333] sorafenib,[394,463] lenvatinib,[466] and pazopanib[465] in MTC. Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.[357,360,392,395] Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.[357]

Novel therapies and the management of aggressive MTC have been reviewed.[315,407,470-473] 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.[461] A phase 2 trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with 131I.[474] Overall survival was improved in the subset of patients with increased calcitonin doubling times.[475]

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas (ATCs) are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[476] Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[477] Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[126,477] The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.[476,478] As previously mentioned, anaplastic carcinoma is the least common type of thyroid carcinoma. An average of 63,229 patients/year were diagnosed with thyroid carcinoma between 2010 to 2014. Of these 63,229 patients, only 514 patients (0.8%) had anaplastic carcinoma.[7]

Approximately 50% of patients with ATC have either a prior or coexistent differentiated carcinoma. Anaplastic carcinoma develops from more differentiated tumors as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor protein.[479] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Iodine deficiency is associated with ATC. More than 80% of patients with ATC have a history of goiter.[478,480,481] Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, 131I imaging cannot be used and RAI treatment is not effective in these patients with ATC.[478]

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

Diagnosis

The diagnosis of ATC is usually established by core or surgical biopsy. If FNA is suspicious or not definitive, core or surgical biopsy should be performed to establish the diagnosis of ATC.[478] The appearance of ATCs varies widely; many ATCs have mixed morphologies. The most common morphology is biphasic spindle and giant cell tumor. Molecular techniques are not recommended for diagnosis of ATC.[478] Sometimes it is difficult to discriminate between ATC and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[112,478] Diagnostic procedures include a CBC with differential, comprehensive chemistry, TSH level, direct exam of larynx, and imaging studies. Neck ultrasound can rapidly assess tumor extension and invasion.[482] CT scans of the head, neck, chest, abdomen, and pelvis can accurately determine the extent of the thyroid tumor and identify tumor invasion of the great vessels and upper aerodigestive tract structures.[484] PET/CT scans from skull base to mid-thigh are recommended to accurately stage the patient. Bone metastases are usually lytic. Evaluation of vocal cord mobility can also be considered. All ATCs are considered stage IV (A, B, or C) (see Table 1 in the NCCN Guidelines for Thyroid Carcinoma). The T4 category includes: T4a tumors that are intrathyroidal and T4b tumors that are extrathyroidal. Clinically apparent anaplastic tumors are usually unresectable.

Prognosis

No curative therapy exists for ATC; it is almost uniformly fatal.[485,486] The median survival from diagnosis is about 5 months.[478,487] The 1-year survival rate is about 20%.[483,487] Death is attributable to upper airway obstruction and suffocation (often despite tracheostomy) in 50% of these patients; in the remaining patients, death is attributable to complications of local and distant disease and/or therapy.[488] Patients with disease confined to the neck at diagnosis have a mean survival of 8 months compared with 3 months if the disease extends beyond the neck.[489] Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, WBC count ≥10,000 mm^3, and dyspnea as a presenting symptom.[490,491]

Treatment

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

Surgery

Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.[476] Before resection is attempted, the extent of disease—particularly in the larynx, trachea, and neck—should be accurately assessed by a very experienced surgeon who is capable of performing extensive neck dissections if necessary. However, most patients with ATC have unresectable or metastatic disease. The patency of the airway should be assessed throughout the patient's course.[488] If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with selective resection of all involved local or regional structures and nodes. Total thyroidectomy with attempted complete tumor resection has not been shown to prolong survival except for the few patients whose tumors are small and confined entirely to the thyroid or readily excised structures.[487,489,493,494] Patients need to receive levothyroxine if total thyroidectomy is done.

Radiation Therapy

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

Systemic Therapy

Treatment with single-drug chemotherapy is not very effective, although some patients may show disease response or have stable disease.[478,499] Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year.[500] Distant metastases then become the leading cause of death.[501] Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin-based regimens, followed by debulking surgery in responsive patients or other multimodality approaches.[499,502-504] IMRT may be useful to reduce toxicity.[445,478,505-509] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival.

Systemic therapy recommendations are described in the algorithm (see *Systemic Therapy for Anaplastic Thyroid Carcinoma* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[478,510] Recommended regimens include paclitaxel and carboplatin combinations, docetaxel and doxorubicin combinations, paclitaxel alone, or doxorubicin alone.[478,511] The dosage and frequency of administration of all the recommended systemic therapy agents are provided in the algorithm. Either concurrent chemoradiation or chemotherapy alone regimens may be used depending on the clinical setting; however, chemoradiation is generally more toxic. If using chemoradiation, the ATA Guidelines recommend using weekly chemotherapy regimens.[478] Chemotherapy alone can be considered for patients with unresectable or metastatic disease. Single-agent doxorubicin is the only agent that is approved by the FDA for ATC.[478] Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease.[512-514] If weekly paclitaxel is used, the ATA Guidelines recommend using paclitaxel at 60 to 90 mg/m^2 IV weekly and not the dose previously reported in the study by Ain et al.[478,514]

Given the poor outcome with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials. Previous clinical trials for ATC have tested therapies including fosbretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin [EPC2407], which are vascular disrupting agents), efatutazone (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.[510,515-522] Outside of clinical trials, targeted therapies are not currently recommended in the NCCN Guidelines for patients with ATC, although some are recommended for patients with papillary, follicular, Hürthle cell, or medullary carcinoma. A trial in 80 patients (FACT) reported that the addition of fosbretabulin—to a carboplatin/paclitaxel regimen—resulted in a nonsignificant increase in median survival (5.2 vs. 4.0 months).[510,523]

Multimodality therapy is recommended in patients with locally resectable disease (see *Primary Treatment* in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[478,505,510,524-528] Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN Panel acknowledged that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported.[529] Preliminary data suggest that ALK inhibitors may be effective in a subset of patients with papillary thyroid cancer who have ALK gene fusions; however, these ALK gene fusions are rarely reported in patients with ATC.[345-348] *BRAF* mutations have been reported in patients with ATC.[482,530-532]

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. 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/.

8. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28055103.

9. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010:1-646.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. Wilhelm S. Evaluation of thyroid incidentaloma. Surg Clin North Am 2014;94:485-497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24857572.

18. 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.

19. Ito Y, Tomoda C, Uruno 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

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. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474385.

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 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 chornobyl 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.

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 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.

80. Cibas ES, Ali SZ, Conference NCITFSotS. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol 2009;132:658-665. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19846805.

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. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. J Clin Oncol 2015;33:42-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25332244.

94. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA 2013;309:1493-1501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23571588.

95. Gouveia C, Can NT, Bostrom A, et al. Lack of association of BRAF mutation with negative prognostic indicators in papillary thyroid carcinoma: the University of California, San Francisco, experience. JAMA Otolaryngol Head Neck Surg 2013;139:1164-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24030686.

96. Elisei R, Ugolini C, Viola D, et al. BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. J Clin Endocrinol Metab 2008;93:3943-3949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18682506.

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. 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.

107. 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.

108. 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.

109. Wong LQ, Baloch ZW. Analysis of the bethesda system for reporting thyroid cytopathology and similar precursor thyroid cytopathology reporting schemes. Adv Anat Pathol 2012;19:313-319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22885380.

110. Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol 2012;56:333-339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22846422.

111. 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.

112. 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.

113. Seethala RR, Asa SL, Carty SE, et al. Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland. Based on AJCC/UICC TNM, 7th edition: Protocol web posting date: January 2016: College of American Pathologists; 2016. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-thyroid-16protocol-3200.pdf.

114. 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.

115. 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.

116. 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.

117. 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.

118. Yassa L, Cibas ES, Benson CB, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer 2007;111:508-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17999413.

119. 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.

120. Brauer VF, Eder P, Miehle K, et al. Interobserver variation for ultrasound determination of thyroid nodule volumes. Thyroid

2005;15:1169-1175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16279851.

121. 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.

122. 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.

123. 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.

124. 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.

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

130. 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.

131. Samuel AM, Rajashekharrao 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.

132. 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.

133. Hay ID, Bergstralh 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.

134. Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery 1995;118:1131-1136; discussion 1136-1138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7491533.

135. Cady B. Staging in thyroid carcinoma. Cancer 1998;83:844-847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9731884.

136. 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.

137. 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.

138. 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.

139. 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.

140. 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.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. LiVolsi VA. Follicular lesions of the thyroid. In: LiVolsi VA, ed. Surgical Pathology of the Thyroid. Philadelphia: WB Saunders; 1990:173-212.

147. LiVolsi VA. Papillary lesions of the thyroid. In: LiVolsi VA, ed. Surgical Pathology of the Thyroid. Philadelphia: WB Saunders; 1990:136-172.

148. 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.

149. 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.

150. 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 Endocrinol Metab 2010;95:4197-4205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20631031.

151. 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.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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.

161. 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.

162. 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.

163. 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.

164. 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.

165. Brennan MD, Bergstralh 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.

166. 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.

167. 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.

168. Belchetz 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. Ruegemer JJ, Hay ID, Bergstralh 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.

174. 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.

175. 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.

176. 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.

177. 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.

178. 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.

179. Hay ID. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990;19:545-576. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2261906.

180. 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.

181. 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.

182. 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.

183. 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.

184. 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.

185. 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.

186. 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.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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.

192. 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.

193. Greene FL, Page DL, Fleming ID. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; 2002.

194. Fleming ID, Cooper JS, Henson DE. AJCC Cancer Staging Manual, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 1997.

195. 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.

196. 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.

197. 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.

198. 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.

199. 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.

200. 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.

201. 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.

202. 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.

203. 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.

204. Tuttle RM. Risk-adapted management of thyroid cancer. Endocr Pract 2008;14:764-774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18996800.

205. Bilimoria 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.

206. 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.

207. Hay ID, Grant CS, Bergstralh 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.

208. 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.

209. 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.

210. 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.

211. 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.

212. 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.

213. Mazzaferri EL. Managing thyroid microcarcinomas. Yonsei Med J 2012;53:1-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22187228.

214. 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.

215. 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.

216. 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.

217. 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.

218. 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.

219. 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.

220. 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.

221. 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.

222. 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.

223. 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.

224. 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.

225. Pacini F, Elisei R, Capezzone 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.

226. 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.

227. 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.

228. 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.

229. 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.

230. 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.

231. 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.

232. 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.

233. 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.

234. 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.

235. 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.

236. 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.

237. 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.

238. 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.

239. 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.

240. 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.

241. 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.

242. 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.

243. Schvartz C, Bonnetain 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.

244. 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.

245. 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.

246. 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.

247. 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.

248. 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.

249. 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.

250. 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.

251. 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.

252. Amdur RJ, Mazzaferri EL. Essentials of Thyroid Cancer Management. New York: Springer Science; 2005.

253. 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.

254. 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.

255. 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.

256. 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.

257. 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.

258. 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.

259. 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.

260. 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.

261. 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.

262. 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.

263. 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.

264. Sherman SI, Tielens 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.

265. 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.

266. 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.

267. 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.

268. 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.

269. 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.

270. 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.

271. 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.

272. 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 misclassifications. J Clin Endocrinol Metab 2014;99:4589-4599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25226290.

273. 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.

274. 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.

275. 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.

276. 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.

277. 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.

278. 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.

279. 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.

280. 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.

281. 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.

282. 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.

283. 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.

284. 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.

285. 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.

286. 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.

287. Quan ML, Pasieka JL, Rorstad O. Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: a 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.

288. 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.

289. 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.

290. 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.

291. 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.

292. 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.

293. 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.

294. 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.

295. 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.

296. 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.

297. 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.

298. 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.

299. 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.

300. 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.

301. 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.

302. Expert Panel on Radiation Oncology-Bone M, Lo SS, Lutz ST, et al. ACR Appropriateness Criteria (R) spinal bone metastases. J Palliat Med 2013;16:9-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23167547.

303. 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.

304. 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.

305. 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.

306. 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.

307. 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.

308. 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.

309. 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.

310. 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.

311. 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.

312. 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.

313. 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.

314. 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.

315. 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.

316. 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.

317. 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.

318. Wang E, Karedan T, Perez CA. New insights in the treatment of radioiodine refractory differentiated thyroid carcinomas: to lenvatinib and beyond. Anticancer Drugs 2015;26:689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25974026.

319. 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.

320. 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.

321. 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.

322. 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.

323. 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.

324. 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.

325. 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.

326. 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.

327. 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.

328. 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.

329. 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.

330. 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.

331. 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.

332. 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.

333. Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid 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.

334. 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.

335. 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.

336. 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.

337. 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.

338. 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.

339. Shah MH, De Souza J, Wirth L, et al. Cabozantinib in patients with radioiodine-refractory differentiated thryoid cancer who progressed on prior VEGFR-targeted therapy: results of NCI- and ITOG-sponsored multicenter phase II clinical trial [abstract]. 15th International Thyroid Congress 2015;Oral Abstract 73. Available at: http://online.liebertpub.com/doi/pdfplus/10.1089/thy.2015.29004.abstracts.

340. 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.

341. 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.

342. 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.

343. 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.

344. 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.

345. 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.

346. 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.

347. 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.

348. 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.

349. 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.

350. 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.

351. 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.

352. 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.

353. 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.

354. 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.

355. 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.

356. 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.

357. 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.

358. 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.

359. 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.

360. 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.

361. 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.

362. 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.

363. 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.

364. 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.

365. 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.

366. 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.

367. 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.

368. 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.

369. 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.

370. 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.

371. 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.

372. 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.

373. 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.

374. 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.

375. 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.

376. 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.

377. 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.

378. 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.

379. 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.

380. 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.

381. 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.

382. 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.

383. 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.

384. 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.

385. 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.

386. 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.

387. 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.

388. 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.

389. Rosen LS, Gordon D, Tchekmedyian 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.

390. 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.

391. 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.

392. 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.

393. 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.

394. 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.

395. 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.

396. Crouzeix G, Michels JJ, Sevin E, et al. Unusual short-term complete response to two regimens of cytotoxic chemotherapy in a patient with poorly differentiated thyroid carcinoma. J Clin Endocrinol Metab 2012;97:3046-3050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22723320.

397. Cohen EE, Needles BM, Cullen KJ, et al. Phase 2 study of sunitinib in refractory thyroid cancer [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 6025. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/6025.

398. Fagin JA, Tuttle RM, Pfister DG. Harvesting the low-hanging fruit: kinase inhibitors for therapy of advanced medullary and nonmedullary thyroid cancer. J Clin Endocrinol Metab 2010;95:2621-2624. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20525911.

399. 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.

400. 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.

401. 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.

402. 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.

403. 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.

404. 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.

405. 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.

406. 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.

407. 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.

408. 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.

409. 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.

410. Gagel RF, Cote GJ. Pathogenesis of medullary thyroid carcinoma. In: JA F, ed. Thyroid Cancer. Boston/Dordrecht/London: Kluwer Academic; 1998:85-103.

411. 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.

412. 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.

413. 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.

414. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. Medicine (Baltimore) 1984;63:319-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6503683.

415. 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.

416. 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.

417. 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.

418. 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.

419. 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.

420. 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.

421. 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.

422. 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.

423. 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.

424. 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.

425. 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.

426. 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.

427. 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.

428. 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.

429. 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.

430. 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.

431. 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.

432. 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.

433. 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.

434. 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.

435. 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.

436. 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.

437. 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.

438. 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.

439. 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.

440. 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.

441. 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.

442. 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.

443. 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.

444. 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.

445. 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.

446. 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.

447. 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.

448. 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.

449. 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.

450. 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.

451. 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.

452. 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.

453. 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.

454. 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.

455. 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.

456. 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.

457. 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.

458. Haraldsdottir S, Shah MH. An update on clinical trials of targeted therapies in thyroid cancer. Curr Opin Oncol 2014;26:36-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24240178.

459. Viola D, Cappagli V, Elisei R. Cabozantinib (XL184) for the treatment of locally advanced or metastatic progressive medullary thyroid cancer. Future Oncol 2013;9:1083-1092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23902240.

460. 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.

461. 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.

462. 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.

463. 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.

464. 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.

465. 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.

466. 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.

467. 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.

468. 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.

469. 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.

470. 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.

471. Santarpia L, Ye L, Gagel RF. Beyond RET: potential therapeutic approaches for advanced and metastatic medullary thyroid carcinoma. J Intern Med 2009;266:99-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19522829.

472. 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.

473. 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.

474. 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.

475. 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.

476. 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.

477. 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.

478. 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.

479. 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.

480. Maatouk J, Barklow TA, Zakaria W, Al-Abbadi 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.

481. 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.

482. 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.

483. 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.

484. 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.

485. 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.

486. 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.

487. 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.

488. Shaha AR. Airway management in anaplastic thyroid carcinoma. Laryngoscope 2008;118:1195-1198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18438260.

489. 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.

490. 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.

491. 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.

492. 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.

493. 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.

494. 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.

495. 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.

496. 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.

497. 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.

498. 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.

499. 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.

500. De Crevoisier R, Baudin E, Bachelot 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.

501. 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.

502. 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.

503. 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.

504. 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.

505. 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.

506. 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.

507. 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.

508. 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.

509. 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.

510. 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.

511. 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.

512. 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.

513. 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.

514. 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.

515. 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.

516. 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.

517. 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.

518. 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.

519. 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.

520. 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.

521. 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.

522. 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.

523. 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.

524. 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.

525. 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.

526. 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.

527. 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.

528. 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.

529. 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.

530. 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.

531. 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.

532. 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.