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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thyroid Carcinoma

Version 2.2013

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Clinical Trials: The NCCN believes that the best management for any cancer patient 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

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The 2.2013 version of the NCCN Guidelines for Thyroid Carcinoma represents the addition of the Discussion text correspondent to the changes in the algorithm (MS-1).

Updates in Version 1.2013 of the NCCN Thyroid Carcinoma Guidelines from Version 3.2012 include:

Thyroid Carcinoma Nodule Evaluation
THYR-3
- Follicular or Hürthle cell neoplasm: The pathway was revised to include molecular diagnostics. The following was added "Consider molecular diagnostics" along with corresponding recommendations.
- Follicular lesion of undetermined significance pathway:
  ➤ The following treatment recommendations were added "Consider molecular diagnostics" and "Observe".
  ➤ The following recommendation was modified: "Repeat FNA ~~observe~~ or consider surgery based on clinical grounds concerning growth or suspicious sonographic findings".
- Footnote h was revised to include the following statement: "If molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation."

Papillary Carcinoma
PAP-1
- Diagnostic procedures:
  ➤ First bullet: Thyroid ultrasound including lateral neck.." changed to "Thyroid and neck ultrasound (including central and lateral compartments)..."
  ➤ Third bullet changed to "Consider evaluation of vocal cord mobility". (Also for FOLL-1 and HÜRT-1)
- Footnote b changed from "Use of iodinated contrast will delay treatment with RAI but may be required for fixed, bulky, or substernal lesions" to "Use of iodinated contrast will delay treatment with RAI but is required for optimal cervical imaging using CT." (Also for FOLL-1 and HÜRT-1)

PAP-2
- Papillary carcinoma found post-lobectomy; Second column; First bullet: "Thyroid and neck ultrasound..." changed to "Thyroid and neck ultrasound (including central and lateral compartments)..."
- Third column; Top pathway: "Confirmed contralateral disease" was added.
- "Tumor 1-4 cm in diameter or Aggressive variant" pathway; Fifth column; After Observe: Suppress TSH with levothyroxine" changed to "Consider levothyroxine therapy to keep TSH low or normal".

PAP-3 (Also for FOLL-2 and HÜRT-2)
- The "No gross residual disease in neck" pathways: The recommendations about clinical indications for RAI therapy were removed and placed on a new page "Decision making for initial adjuvant or therapeutic administration of RAI".

PAP-4 (Also for FOLL-3 and HÜRT-3)
- A new page was added to help clinicians decide whether to administer postoperative RAI, "Decision making for initial adjuvant or therapeutic administration of RAI".

PAP-5 (Also for FOLL-4 and HÜRT-4)
- 2-12 week post-thyroidectomy; No gross residual disease pathway; Second column: "Clinical indication for radioiodine therapy" changed to "Radioiodine therapy based on clinical indications".
- Third column; Top pathway wording was modified as follows: "Tg < 1 ng/mL with negative antithyroglobulin antibodies and negative radioiodine imaging ~~negative~~".
- Fourth column heading revised as follows: "Postsurgical Therapy for Patients Being Considered for RAI Therapy".
- Suspected or proven thyroid bed uptake pathway; Fourth column: "Consider adjuvant radioiodine ablation to destroy residual thyroid function; post-treatment imaging" changed to "Consider ~~adjuvant~~ radioiodine ablation to destroy residual thyroid ~~function~~ tissue; post-treatment imaging".

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Papillary Carcinoma---continued
PAP-6 (Also for FOLL-5 and HÜRT-5)
• **Surveillance and Maintenance**
  ➤ Fourth bullet was revised as follows: "Consider TSH-stimulated radioiodine imaging in high-risk patients, patients with previous RAI avid metastases, or patients with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), ~~abnormal~~ stable or rising antithyroglobulin antibodies, or abnormal ultrasound during surveillance"
  ➤ Fifth bullet was revised as follows: "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)".
  ➤ Sixth bullet was revised as follows: "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, chest CT, FDG-PET/CT)".
  ➤ New bullet was added: "Patients treated with ^{131}I ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative Tg 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 as clinically appropriate, may be considered if clinical suggestion of recurrent disease."
• **Recurrent Disease**
  ➤ Third pathway; Stimulated Tg > 10 ng/mL...:
    ◇ The first bullet was revised as follows: "Stimulated Tg > 10 ng/mL and rising".
    ◇ The treatment recommendation was revised as follows: "Consider radioiodine therapy with 100-150 mCi and post-treatment ^{131}I imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy".
PAP-7 (Also for FOLL-6 and HÜRT-6)
• Metastatic disease; CNS pathway: The following recommendation was removed: "If radioiodine imaging positive, consider radioiodine treatment with steroid prophylaxis".
• Footnote "r": A link to the NCCN Guidelines for Central Nervous System Cancers was added.
• Footnote "s" was modified: Denosumab and bisphosphonates can be associated with severe hypocalcemia..."

Follicular Carcinoma (Also see the Papillary Carcinoma Updates)
FOLL-1
• Diagnostic Procedures: "Consider lateral neck ultrasound" changed to "Thyroid and neck ultrasound (including central and lateral compartments), if not previously done". (Also for HÜRT-1)

Hürthle Cell Carcinoma (Also see the Papillary Carcinoma Updates)
HÜRT-1
• Primary Treatment: "Total thyroidectomy if invasive cancer..." changed to "Total thyroidectomy if invasive cancer, metastatic disease..."

Medullary Thyroid Carcinoma
MEDU-1
- Additional Workup:
  - Seventh Bullet: "Consider lateral neck ultrasound" changed to "Thyroid and neck ultrasound (including central and lateral compartments); if not previously done".
  - Eight Bullet was modified: "Consider evaluation of vocal cord mobility".

MEDU-2
- This page was revised to address the concept of incomplete thyroidectomy if sporadic disease, no imaging evidence of disease, and calcitonin negative.

MEDU-3
- Germline mutation of RET proto-oncogene; Additional Workup for MEN 2B and MEN2A/Familial medullary: "Neck ultrasound" changed to "Central and lateral neck compartments ultrasound, if not previously done".

MEDU-5
- Basal calcitonin undetectable or CEA within reference range; Observe; Surveillance: Second Bullet: "Consider neck ultrasound" changed to "Consider central and lateral neck compartments ultrasound".

MEDU-6
- Recurrent or Persistent Disease
  - Locoregional:
    - The following recommendation was revised as follows: "Consider EBRT ~~or vandetanib for unresectable symptomatic or structurally progressive disease~~".
    - "Consider cabozantinib (category 1) for unresectable disease that is symptomatic or structurally progressive" was added as an option. Vandetanib changed from category 2A to a category 1 recommendation. Due to these changes, the following recommendation was added: "Consider vandetanib (category 1) or cabozantinib (category 1) for unresectable disease that is symptomatic or structurally progressive".

MEDU-6---continued
- Symptomatic, distant metastasis
  - Vandetanib changed from category 2A to a category 1 recommendation, and the recommendation was modified as follows: "Consider vandetanib (category 1)".
  - The following recommendation was added: "Consider cabozantinib (category 1)".
- Asymptomatic, distant metastases:
  - The recommendation was revised as follows: Consider resection (if possible), ablation (eg, RFA, embolization, or other regional therapy), or vandetanib (category 1), or cabozantinib (category 1) if structurally progressive disease". (vandetanib changed from category 2A to category 1 recommendation)
- Disseminated symptomatic disease
  - Vandetanib changed from category 2A to a category 1 recommendation.
  - Cabozantinib (category 1) was added as a treatment option.
- Footnote "k" is new to the page: *Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
- Footnote "m" was revised as follows: "While not FDA approved for treatment of thyroid cancer, other commercially available small molecule kinase inhibitors (such as sorafenib or sunitinib) can be considered if clinical trials, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib."

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Anaplastic Thyroid Carcinoma
ANAP-1
- Diagnostic Procedures: "Consider bone scan" was removed.
- Locally resectable (rarely encountered) pathway: The recommendation changed from "Consider EBRT (consider hyperfractionation) ± radiosensitizing chemotherapy" to "EBRT (consider hyperfractionation) ± concurrent chemotherapy".
- Third column: The pathway was revised as follows: "Unresectable local tumor ± distant disease".
- "Unresectable local tumor ± distant disease" pathway:
  ◊ "Consider EBRT (consider hyperfractionation) and/or chemotherapy" changed to "Consider EBRT (consider hyperfractionation) ± concurrent chemotherapy."
  ◊ "Consider chemotherapy" was added as a treatment option.
- After "Best Supportive Care" a link to the **NCCN Guidelines for Palliative Care** was added.
- Footnote "b" is new to the page: Consider multidisciplinary evaluation and referral to high-volume center with experience in treating this disease.

ANAP-A---Systemic Therapy for Anaplastic Thyroid Carcinoma
- This is a new page that provides systemic therapy options for the treatment of anaplastic thyroid carcinoma as follows:
  ► Concurrent Chemoradiation Regimens
    ◊ Paclitaxel/Carboplatin
    ◊ Paclitaxel
    ◊ Cisplatin
    ◊ Doxorubicin
  ► Chemotherapy Regimens
    ◊ Paclitaxel/Carboplatin
    ◊ Paclitaxel
    ◊ Doxorubicin

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Thyroid Carcinoma – Nodule Evaluation

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CLINICAL PRESENTATION   **WORKUP**

For thyroid nodule known or suspected on exam or incidental imaging finding:
- **Measure thyroid stimulating hormone (TSH)**
- **Ultrasound of thyroid and central neck**
- **Ultrasound of lateral neck (category 2B)**

Thyroid nodule(s) with low TSH → **Radioiodine imaging**

Autonomously functioning (hot) → **Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)[b]**

Cold or warm →

Consider FNA based on clinical and sonographic features → **See Sonographic Features[b] (THYR-2)**

Thyroid nodule(s) with normal or elevated TSH[a] →

[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 scan or FNA, surveillance should include repeat ultrasound after 6-12 months; if stable for 1-2 years, then subsequent ultrasound can be considered at 3-5 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.

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SONOGRAPHIC FEATURES

Threshold for FNA

Solid nodule
- With suspicious sonographic features[c] $\geq$ **1.0 cm**
- Without suspicious sonographic features[c] $\geq$ **1.5 cm**

Mixed cystic-solid nodule
- With suspicious sonographic features[c] $\geq$ **1.5-2.0 cm**
- Without suspicious sonographic features[c] $\geq$ **2.0 cm**

Spongiform nodule[d] $\geq$ **2.0 cm**

Simple cyst   **Not indicated[e]**

Suspicious cervical lymph node   **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. In patients with high-risk clinical features,[f] evaluations of nodules smaller than listed may be appropriate depending upon 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.

[b]For nodules not meeting criteria for FNA, or nodules that appear to be benign by scan or FNA, surveillance should include repeat ultrasound after 6-12 months; if stable for 1-2 years, then subsequent ultrasound can be considered at 3-5 year intervals.
[c]Suspicious sonographic features: Hypoechoic, microcalcifications, increased central vascularity, infiltrative margins, taller than wide in transverse plane.
[d]Aggregation of multiple microcystic components in more than 50% of the volume of the nodule.
[e]Except as therapeutic modality.
[f]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, Cowden syndrome; personal history of thyroid cancer in lobectomy.

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Thyroid Carcinoma – Nodule Evaluation

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)**

Diagnostic categories for FNA results reflect NCI state of the science conference, available from http://www.cytojournal.com/content/5/1/6. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

Follicular or Hürthle cell neoplasm[g,h] → **Consider molecular diagnostics**

- Molecular diagnostics indicate benign lesion[h] → Observe **or** Consider lobectomy for definitive diagnosis/treatment
- Molecular diagnostics not done, not informative, not indicative of a benign lesion, or suggestive of malignancy → **See Primary Treatment for Papillary (PAP-1) Follicular (FOLL-1) or Hürthle (HÜRT-1)**

Follicular lesion of undetermined significance[h,i]

- Repeat FNA or consider surgery[h] based on clinical grounds concerning growth or suspicious sonographic findings[c,k]
- Consider molecular diagnostics (see pathway above for Follicular or Hürthle cell neoplasm)
- Observe

[c]Suspicious sonographic features: Hypoechoic, microcalcifications, increased central vascularity, infiltrative margins, taller than wide in transverse plane.

[g]Alternative term: Suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 20%-30%.

[h]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 (follicular neoplasm or follicular lesions of undetermined significance) as more likely to be benign or more likely to be malignant. If molecular testing suggests papillary thyroid carcinoma, see (PAP-1). If molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation.

[i]Alternative terms include: Atypia of undetermined significance, rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%-10%.

[k]Observation for lower risk patients with good quality FNA.

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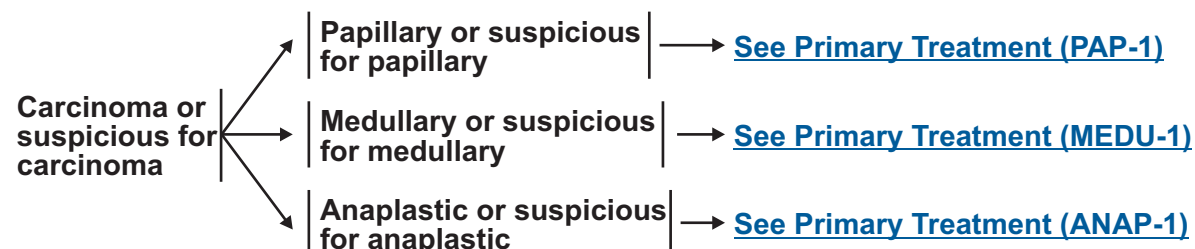
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FNA RESULTS   **TREATMENT**

Thyroid lymphoma ————————————→ **See NCCN Non-Hodgkin's Lymphoma Guideline**

Insufficient biopsy, nondiagnostic

→ Cystic ————————→ **Correlate with ultrasound, re-aspirate suspicious areas**

→ Solid ————————→ **Repeat FNA with ultrasound guidance and immediate cytologic review**
or
Consider surgery

Benign[k] ————————————→ • **Observe[l]**
• **If nodule growth, repeat FNA or consider surgery**

[k]Includes nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, and Hashimoto's thyroiditis. Estimated risk of malignancy is < 1%.

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

Diagnostic categories for FNA results reflect NCI state of the science conference, available from http://www.cytojournal.com/content/5/1/6. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

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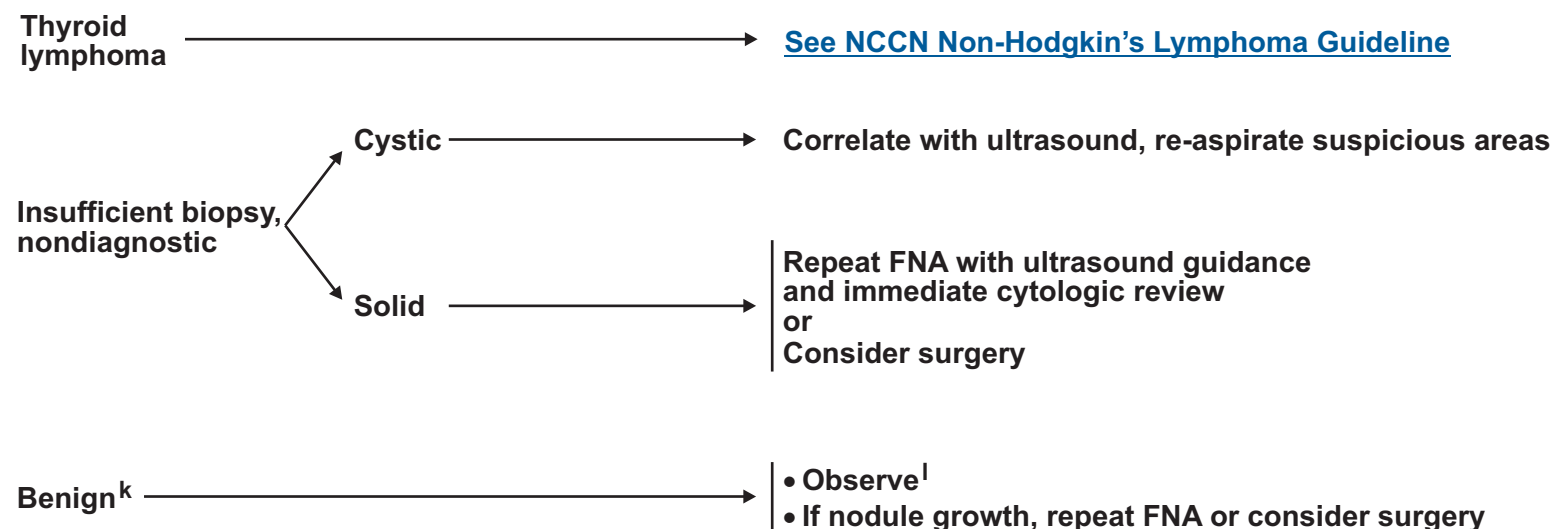
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**NCCN Guidelines Version 2.2013
Thyroid Carcinoma – TSH Suppression**

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PRINCIPLES OF THYROID STIMULATING HORMONE (TSH) SUPPRESSION

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

  - **In general, patients with known 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/day) and vitamin D (1000 units/day).**

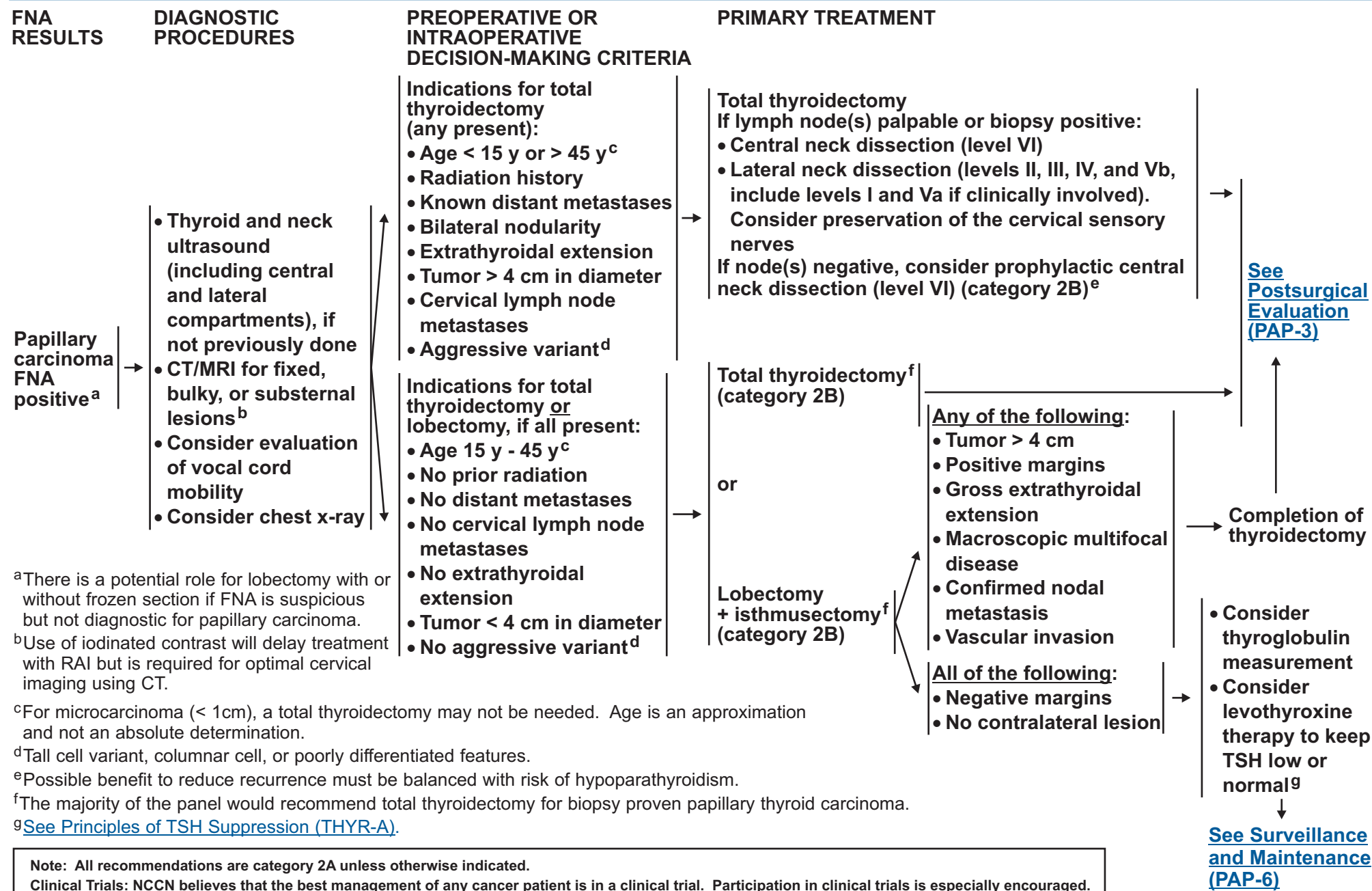**Note: All recommendations are category 2A unless otherwise indicated.**
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THYR-A

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FNA RESULTS

DIAGNOSTIC PROCEDURES

PREOPERATIVE OR INTRAOPERATIVE DECISION-MAKING CRITERIA

PRIMARY TREATMENT

Papillary carcinoma FNA positive[a]

- **Thyroid and neck ultrasound (including central and lateral compartments), if not previously done**
- **CT/MRI for fixed, bulky, or substernal lesions[b]**
- **Consider evaluation of vocal cord mobility**
- **Consider chest x-ray**

Indications for total thyroidectomy (any present):
- **Age < 15 y or > 45 y[c]**
- **Radiation history**
- **Known distant metastases**
- **Bilateral nodularity**
- **Extrathyroidal extension**
- **Tumor > 4 cm in diameter**
- **Cervical lymph node metastases**
- **Aggressive variant[d]**

Total thyroidectomy
If lymph node(s) palpable or biopsy positive:
- **Central neck dissection (level VI)**
- **Lateral neck dissection (levels II, III, IV, and Vb, include levels I and Va if clinically involved). Consider preservation of the cervical sensory nerves**
If node(s) negative, consider prophylactic central neck dissection (level VI) (category 2B)[e]

See Postsurgical Evaluation (PAP-3)

Indications for total thyroidectomy or lobectomy, if all present:
- **Age 15 y - 45 y[c]**
- **No prior radiation**
- **No distant metastases**
- **No cervical lymph node metastases**
- **No extrathyroidal extension**
- **Tumor < 4 cm in diameter**
- **No aggressive variant[d]**

Total thyroidectomy[f] (category 2B)

or

Lobectomy + isthmusectomy[f] (category 2B)

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

Completion of thyroidectomy

All of the following:
- **Negative margins**
- **No contralateral lesion**

- **Consider thyroglobulin measurement**
- **Consider levothyroxine therapy to keep TSH low or normal[g]**

See Surveillance and Maintenance (PAP-6)

[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 will delay treatment with RAI but is required for optimal cervical imaging using CT.

[c]For microcarcinoma (< 1cm), a total thyroidectomy may not be needed. Age is an approximation and not an absolute determination.

[d]Tall cell variant, columnar cell, or poorly differentiated features.

[e]Possible benefit to reduce recurrence must be balanced with risk of hypoparathyroidism.

[f]The majority of the panel would recommend total thyroidectomy for biopsy proven papillary thyroid carcinoma.

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

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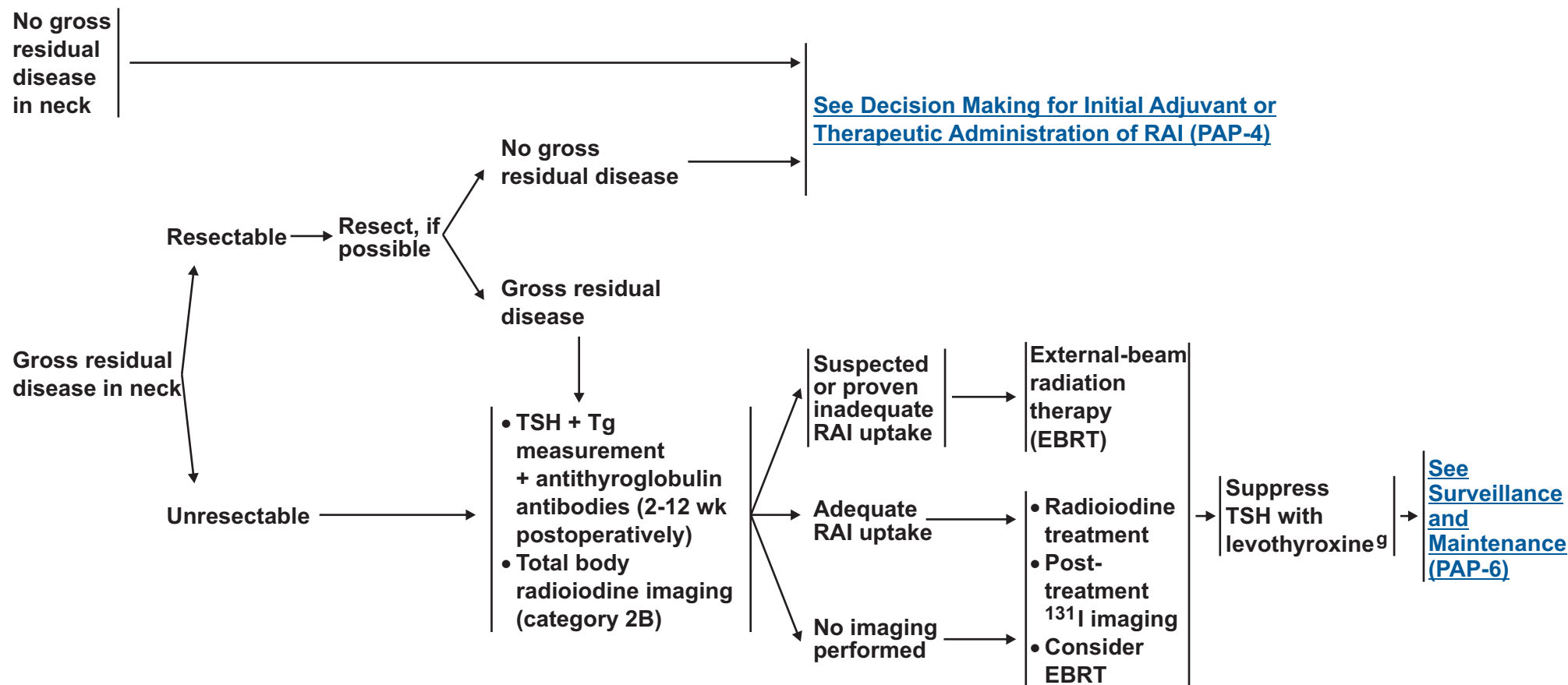# Thyroid Carcinoma – Papillary Carcinoma

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CLINICAL PRESENTATION

PRIMARY TREATMENT

Papillary carcinoma found post-lobectomy

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

Any of the following:
- Tumor > 4 cm
- Positive margins
- Gross extra-thyroidal extension
- Macroscopic multifocal disease
- Confirmed nodal metastasis
- Confirmed contralateral disease
- Vascular invasion

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

Tumor 1-4 cm in diameter or Aggressive variant [d]

→ Completion of thyroidectomy (category 2B)

or

Observe [h] → Consider levothyroxine therapy to keep TSH low or normal [g]

→ **See Postsurgical Evaluation (PAP-3)**

→ **See Surveillance and Maintenance (PAP-6)**

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

→ Observe [h] → Consider levothyroxine therapy to keep TSH low or normal [g] → **See Surveillance and Maintenance (PAP-6)**

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[d] Tall cell variant, columnar cell, or poorly differentiated features.
[g] See Principles of TSH Suppression (THYR-A).
[h] Measurement of thyroglobulin and antithyroglobulin antibodies.

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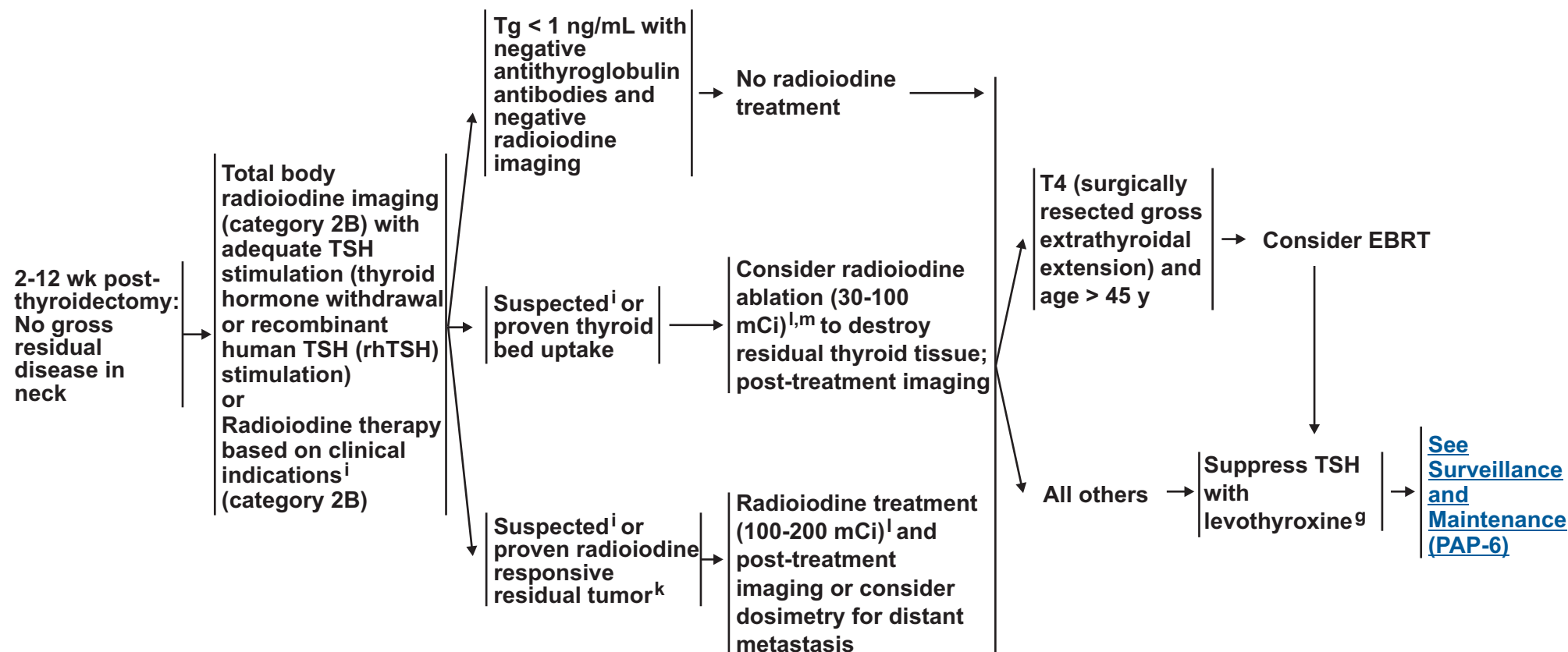Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

POSTSURGICAL EVALUATION

No gross residual disease in neck ──────────────→ See Decision Making for Initial Adjuvant or Therapeutic Administration of RAI (PAP-4)

Gross residual disease in neck

Resectable → Resect, if possible
- No gross residual disease ──→ See Decision Making for Initial Adjuvant or Therapeutic Administration of RAI (PAP-4)
- Gross residual disease

Unresectable →

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

→ Suspected or proven inadequate RAI uptake → External-beam radiation therapy (EBRT)

→ Adequate RAI uptake → • Radioiodine treatment • Post-treatment ^{131}I imaging

→ No imaging performed → • Consider EBRT

→ Suppress TSH with levothyroxine[g] → See Surveillance and Maintenance (PAP-6)

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

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CLINICO-PATHOLOGIC FACTORS

DECISION MAKING FOR INITIAL ADJUVANT OR THERAPEUTIC ADMINISTRATION OF RAI

RAI recommended (if any present):
- **Gross extrathyroidal extension**
- **Primary tumor > 4 cm**
- **Known or suspected distant metastases**

→ RAI therapy ⟶ **See PAP-5**

RAI selectively recommended (if any present): [i]
- Primary tumor 1-4 cm
- High-risk histology
- Vascular invasion
- Cervical lymph node metastases
- Minor extrathyroidal extension
- Multifocality
- Inappropriate postoperative Tg

→ RAI
or
Further evaluation to determine need for RAI ⟶ **See PAP-5**

→ Follow-up without RAI ablation ⟶ **See PAP-6**

RAI not recommended (if all present): [i]
- **Classic papillary thyroid carcinoma (PTC)**
- **Primary tumor < 1 cm**
- **Intrathyroidal**
- **Unifocal or multifocal**
- **No vascular invasion**
- **Appropriate postoperative Tg**
- **Clinical N0**
- **Clinical M0**

→ Follow-up without RAI ablation ⟶ **See PAP-6**

[i] RAI ablation is not required in patients with classic PTC that have T1b/T2 (1-4 cm) cN0 disease or small-volume N1a disease (fewer than 3-5 metastatic lymph nodes <1 cm in diameter), particularly if the postoperative Tg is < 1 ng/mL in the absence of interfering anti-Tg antibodies. However, RAI ablation is recommended, when the combination of individual clinical factors (such as the size of primary tumor, histology, degree of vascular invasion and/or lymph node metastases, postoperative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.

> **Note: All recommendations are category 2A unless otherwise indicated.**
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**POSTSURGICAL THERAPY FOR PATIENTS
BEING CONSIDERED FOR RAI THERAPY**

2-12 wk post-thyroidectomy: No gross residual disease in neck
→
Total body radioiodine imaging (category 2B) with adequate TSH stimulation (thyroid hormone withdrawal or recombinant human TSH (rhTSH) stimulation) or Radioiodine therapy based on clinical indications[i] (category 2B)

- **Tg < 1 ng/mL with negative antithyroglobulin antibodies and negative radioiodine imaging** → **No radioiodine treatment**

- **Suspected[i] or proven thyroid bed uptake** → **Consider radioiodine ablation (30-100 mCi)[l,m] to destroy residual thyroid tissue; post-treatment imaging**

- **Suspected[i] or proven radioiodine responsive residual tumor[k]** → **Radioiodine treatment (100-200 mCi)[l] and post-treatment imaging or consider dosimetry for distant metastasis**

→ **T4 (surgically resected gross extrathyroidal extension) and age > 45 y** → **Consider EBRT**

→ **All others** → **Suppress TSH with levothyroxine[g]** → **See Surveillance and Maintenance (PAP-6)**

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

[i] Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

[k] All patients should be examined, and palpable neck metastases or sonographically significant disease should be surgically resected if possible before radioiodine treatment.

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

[m] 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 RAI ablation dose of 30 mCi of ^{131}I may also be considered (category 2B) for patients with T1b/T2 (1-4cm) with small volume N1a disease and for patients with primary tumors less than 4 cm, clinical N0 with minor extrathyroidal extension.

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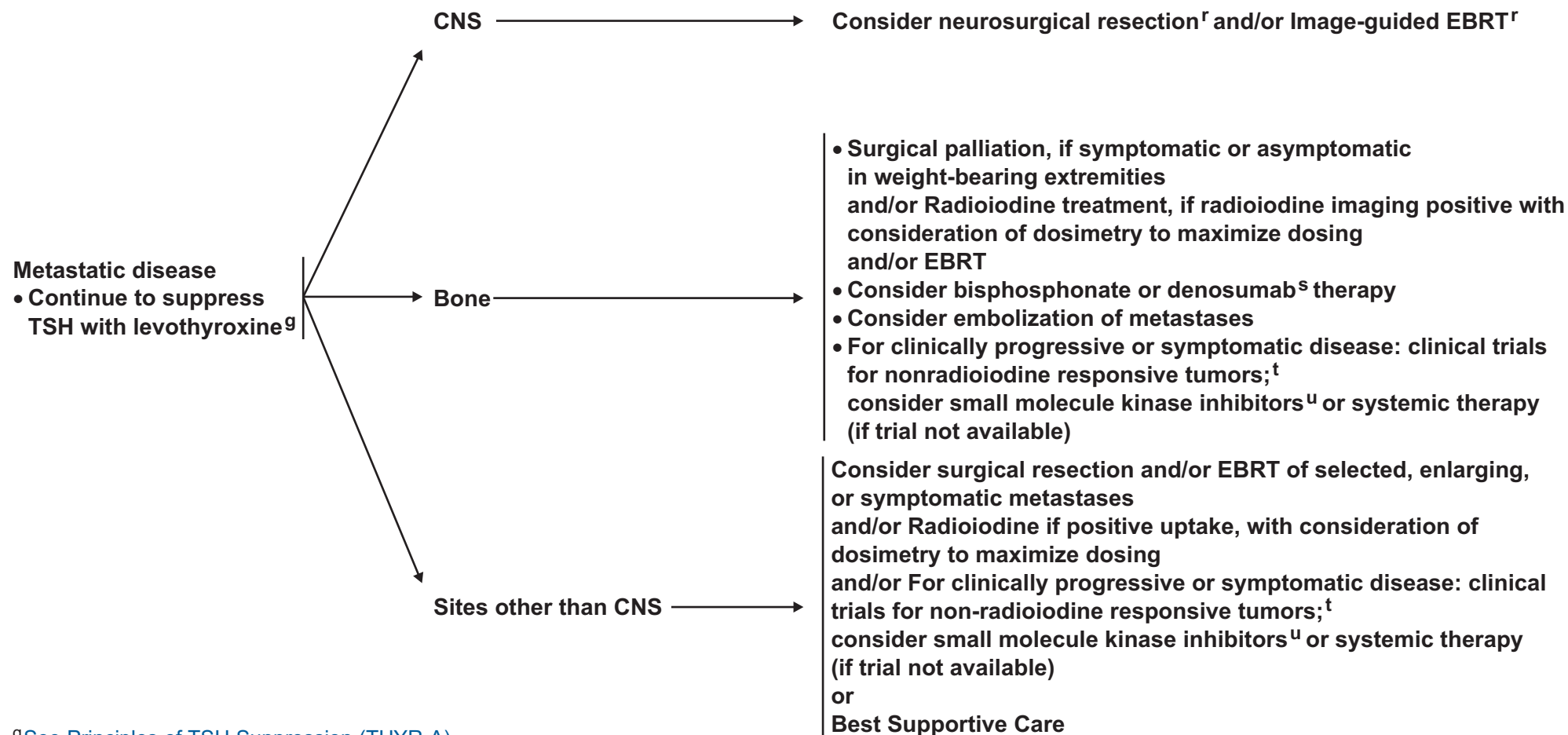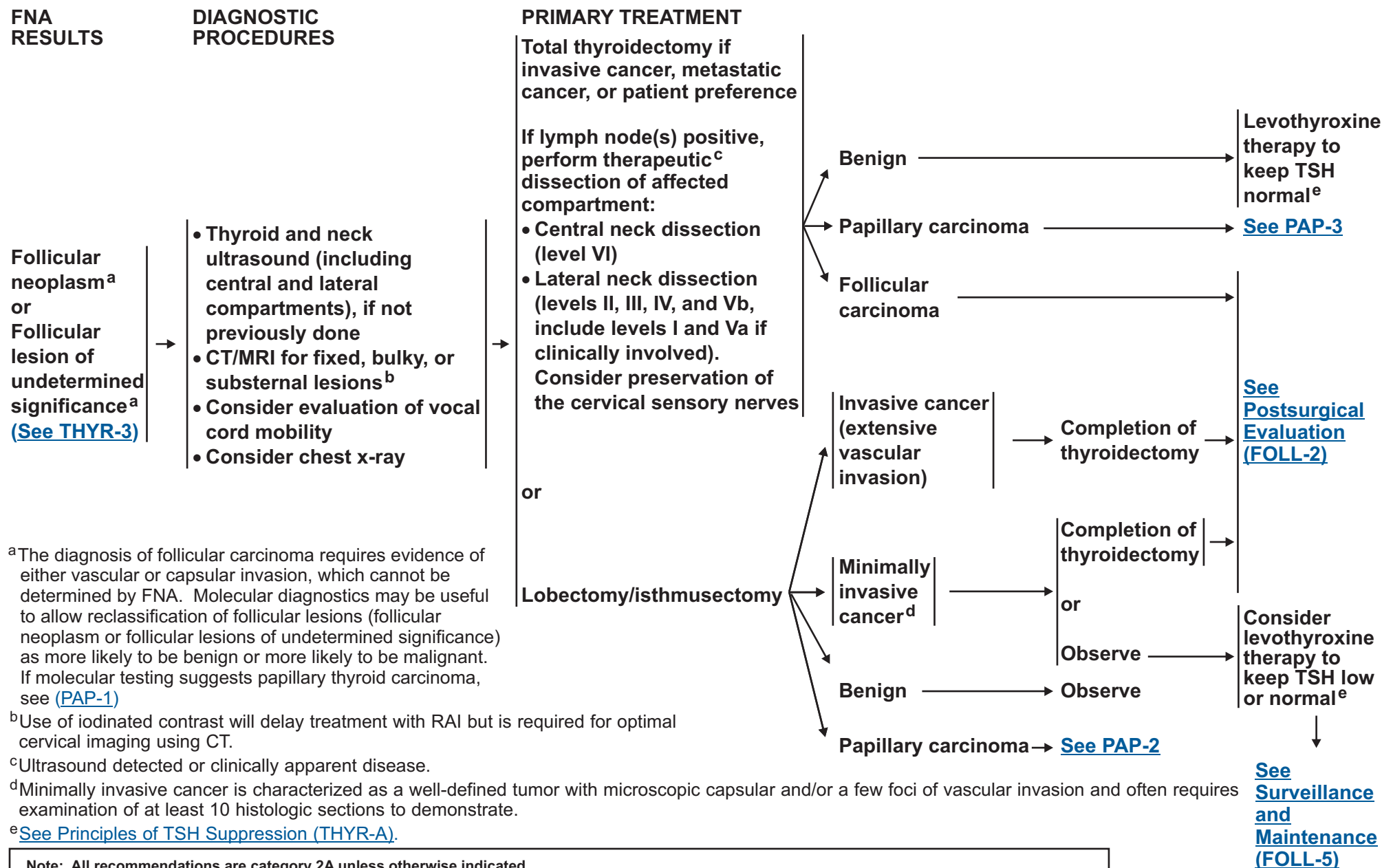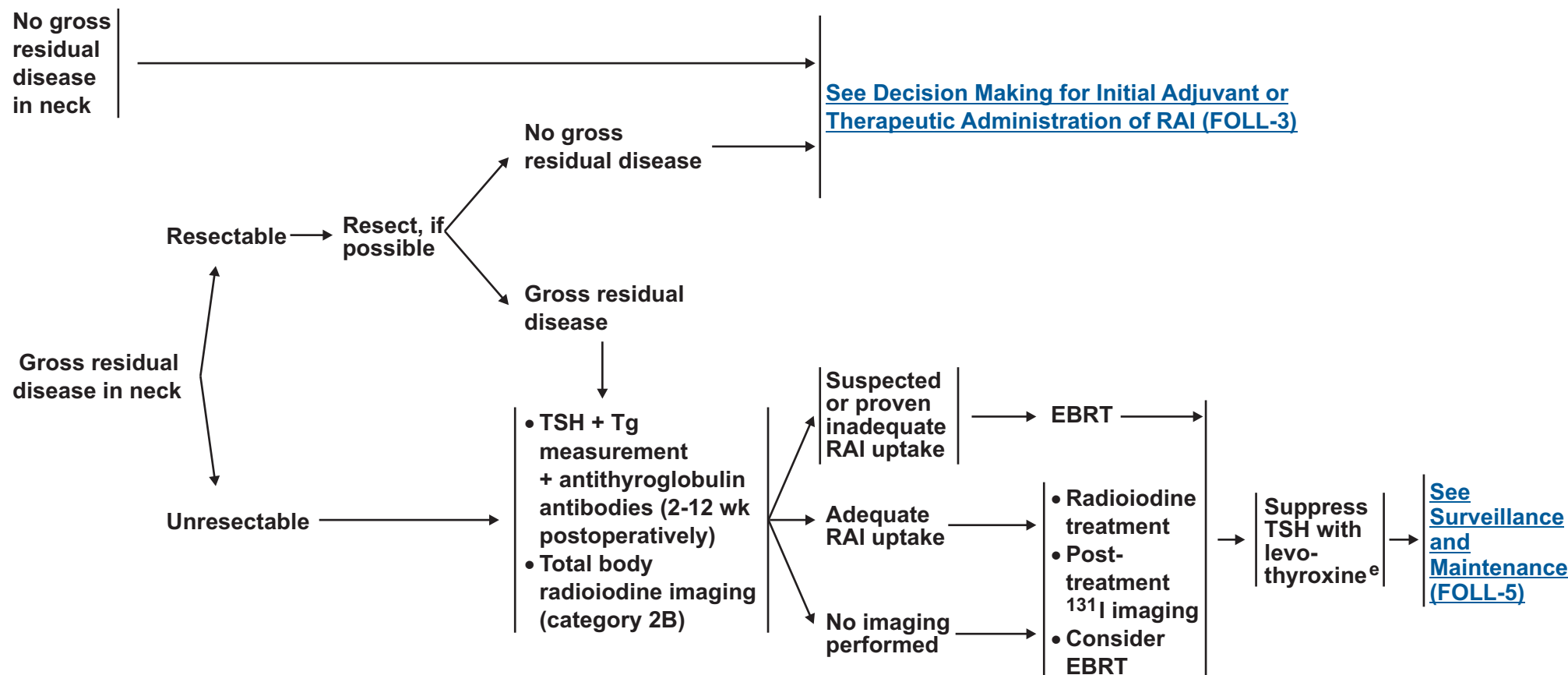> **Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound[n]
- Consider TSH stimulated Tg measurement in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[o]
- Consider TSH-stimulated radioiodine 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
- 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)[p]
- 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, chest CT, FDG-PET/CT)
- Patients treated with ^{131}I ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative Tg 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 as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

RECURRENT DISEASE

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

→ Suppress TSH with levothyroxine[g]

Locoregional recurrence →

Surgery (preferred) if resectable[q] and/or
Radioiodine treatment,[l] if radioiodine imaging positive and/or
EBRT, if radioiodine imaging negative

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

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

Metastatic disease → **See Treatment of Metastases (PAP-7)**

---

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

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

[n] A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

[o] 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. With a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).

[o] 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. With a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).

[p] If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.

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

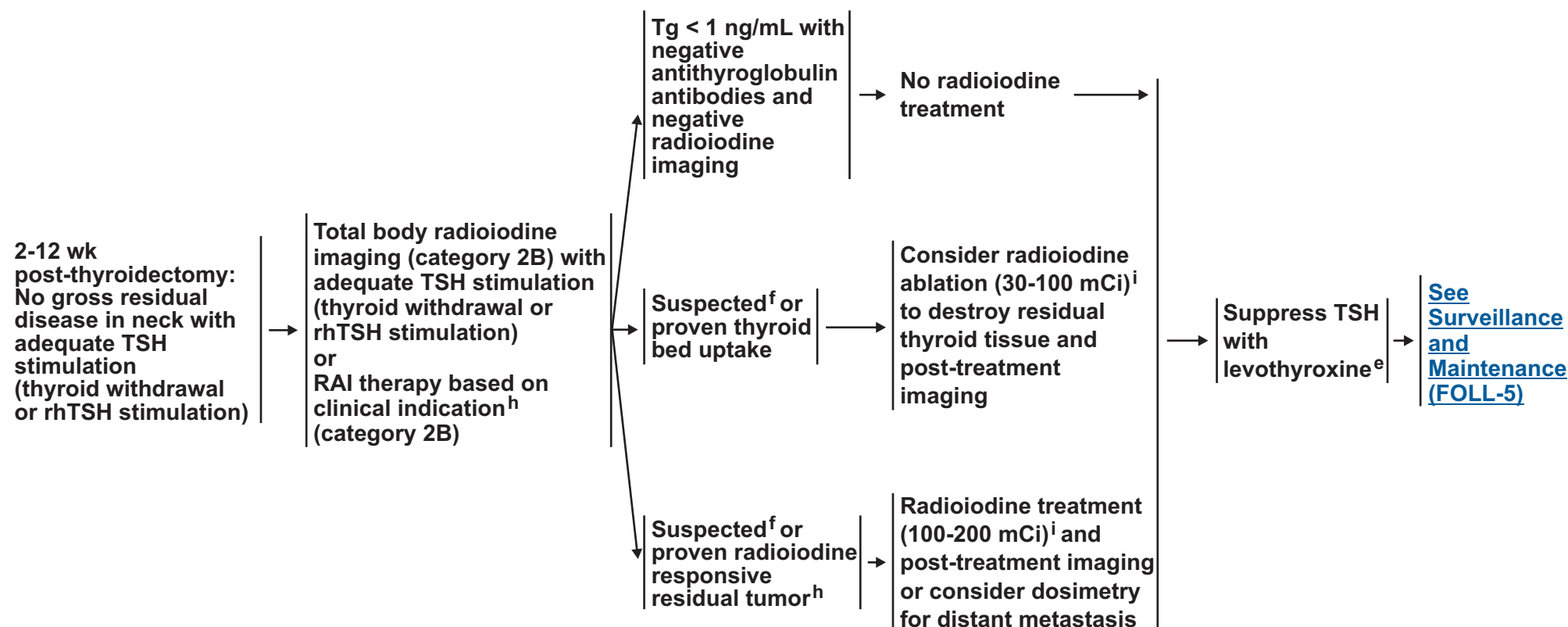Note: All recommendations are category 2A unless otherwise indicated.
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TREATMENT OF METASTASES

Metastatic disease
- **Continue to suppress TSH with levothyroxine[g]**

CNS ⟶ **Consider neurosurgical resection[r] and/or Image-guided EBRT[r]**

Bone ⟶
- **Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities and/or Radioiodine treatment, if radioiodine imaging positive with consideration of dosimetry to maximize dosing and/or EBRT**
- **Consider bisphosphonate or denosumab[s] therapy**
- **Consider embolization of metastases**
- **For clinically progressive or symptomatic disease: clinical trials for nonradioiodine responsive tumors;[t] consider small molecule kinase inhibitors[u] or systemic therapy (if trial not available)**

Sites other than CNS ⟶
Consider surgical resection and/or EBRT of selected, enlarging, or symptomatic metastases and/or Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing and/or For clinically progressive or symptomatic disease: clinical trials for non-radioiodine responsive tumors;[t] consider small molecule kinase inhibitors[u] or systemic therapy (if trial not available) or Best Supportive Care

[g] See Principles of TSH Suppression (THYR-A).
[r] For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred. (See NCCN Guidelines for Central Nervous System Cancers)
[s] Denosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[t] Cytotoxic chemotherapy has shown to have minimal efficacy. Clinical trials investigating novel targeted therapies are ongoing.
   See Clinical trials available at the NCCN member institutions.
[u] While not FDA approved for treatment of thyroid cancer, commercially available small molecule kinase inhibitors (such as sorafenib, sunitinib, or pazopanib [category 2B for pazopanib]) can be considered if clinical trials are not available or appropriate.

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FNA RESULTS

Follicular neoplasm[a] or Follicular lesion of undetermined significance[a] (See THYR-3)

DIAGNOSTIC PROCEDURES

- **Thyroid and neck ultrasound (including central and lateral compartments), if not previously done**
- **CT/MRI for fixed, bulky, or substernal lesions[b]**
- **Consider evaluation of vocal cord mobility**
- **Consider chest x-ray**

PRIMARY TREATMENT

Total thyroidectomy if invasive cancer, metastatic cancer, or patient preference

If lymph node(s) positive, perform therapeutic[c] dissection of affected compartment:
- **Central neck dissection (level VI)**
- **Lateral neck dissection (levels II, III, IV, and Vb, include levels I and Va if clinically involved). Consider preservation of the cervical sensory nerves**

or

Lobectomy/isthmusectomy

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

→ **Papillary carcinoma** → **See PAP-3**

→ **Follicular carcinoma** →

Invasive cancer (extensive vascular invasion) → **Completion of thyroidectomy** →

Minimally invasive cancer[d] → **Completion of thyroidectomy** → **or** **Observe** →

Benign → **Observe**

Papillary carcinoma → **See PAP-2**

→ **See Postsurgical Evaluation (FOLL-2)**

Consider levothyroxine therapy to keep TSH low or normal[e]

→ **See Surveillance and Maintenance (FOLL-5)**

[a] The diagnosis of follicular carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (follicular neoplasm or follicular lesions of undetermined significance) as more likely to be benign or more likely to be malignant. If molecular testing suggests papillary thyroid carcinoma, see (PAP-1)

[b] Use of iodinated contrast will delay treatment with RAI but is required for optimal cervical imaging using CT.

[c] Ultrasound detected or clinically apparent disease.

[d] Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.

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

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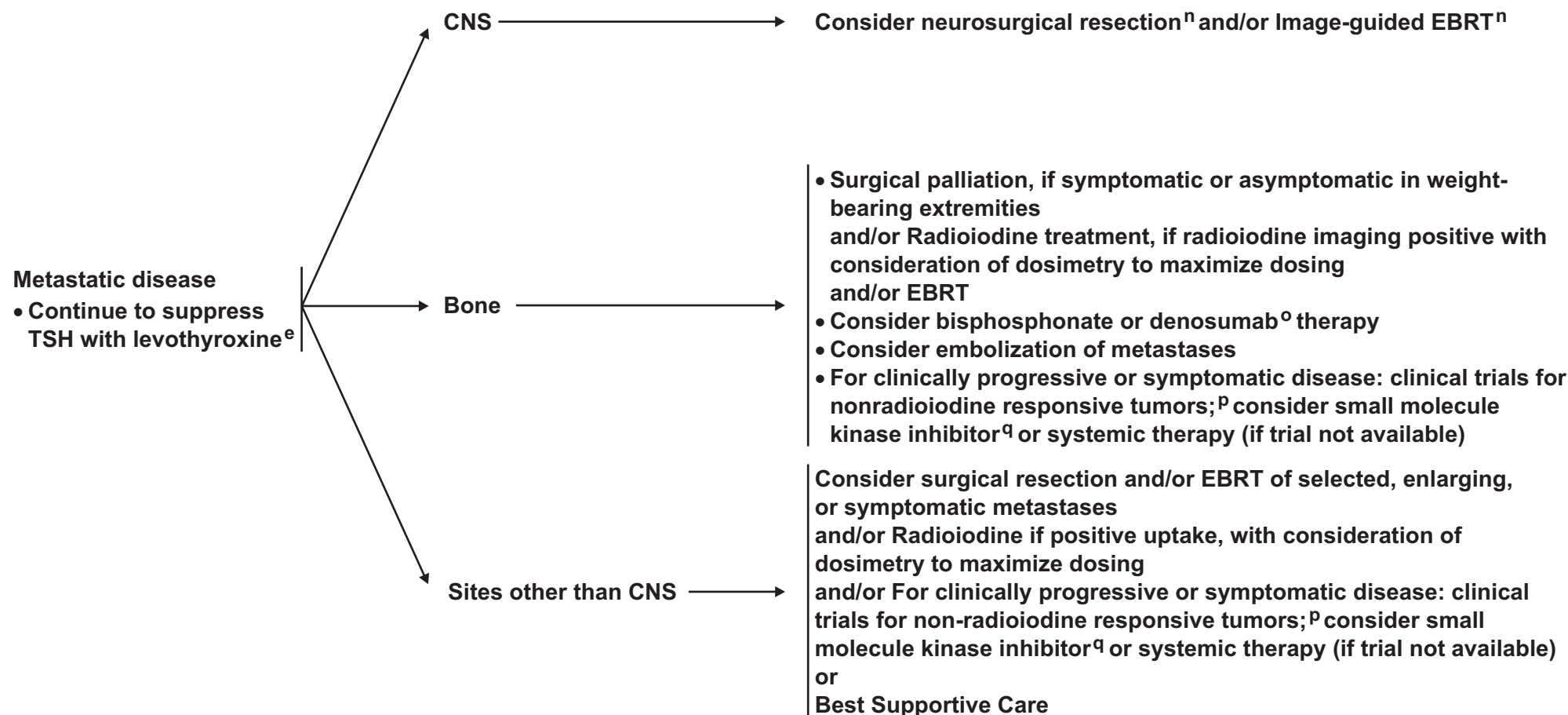Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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POSTSURGICAL EVALUATION

No gross residual disease in neck → See Decision Making for Initial Adjuvant or Therapeutic Administration of RAI (FOLL-3)

Gross residual disease in neck

Resectable → **Resect, if possible**
- **No gross residual disease** → See Decision Making for Initial Adjuvant or Therapeutic Administration of RAI (FOLL-3)
- **Gross residual disease** →

Unresectable →

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

→ **Suspected or proven inadequate RAI uptake** → EBRT →

→ **Adequate RAI uptake** →

→ **No imaging performed** →

- Radioiodine treatment
- Post-treatment ^{131}I imaging
- Consider EBRT

→ Suppress TSH with levo-thyroxine[e] → See Surveillance and Maintenance (FOLL-5)

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

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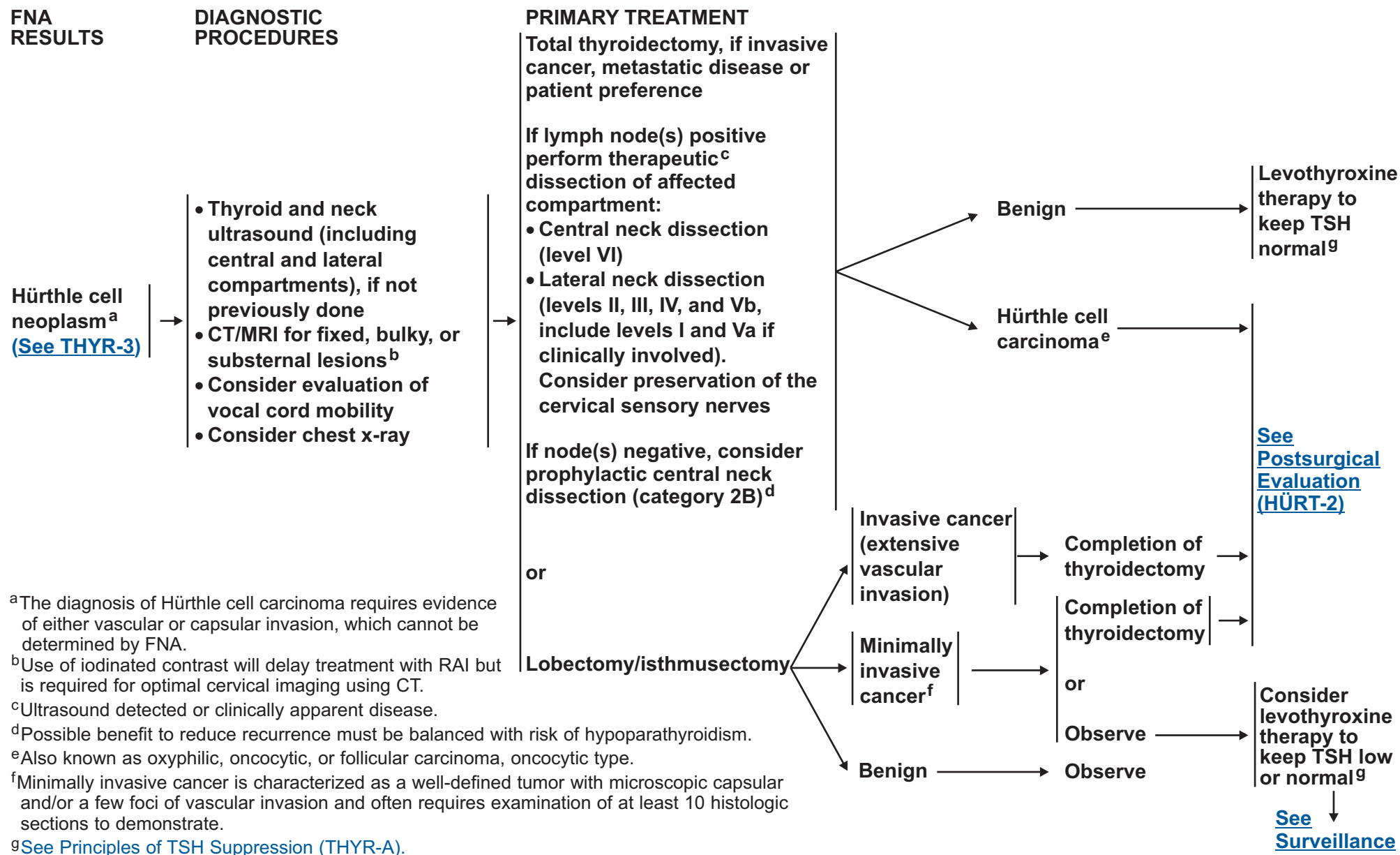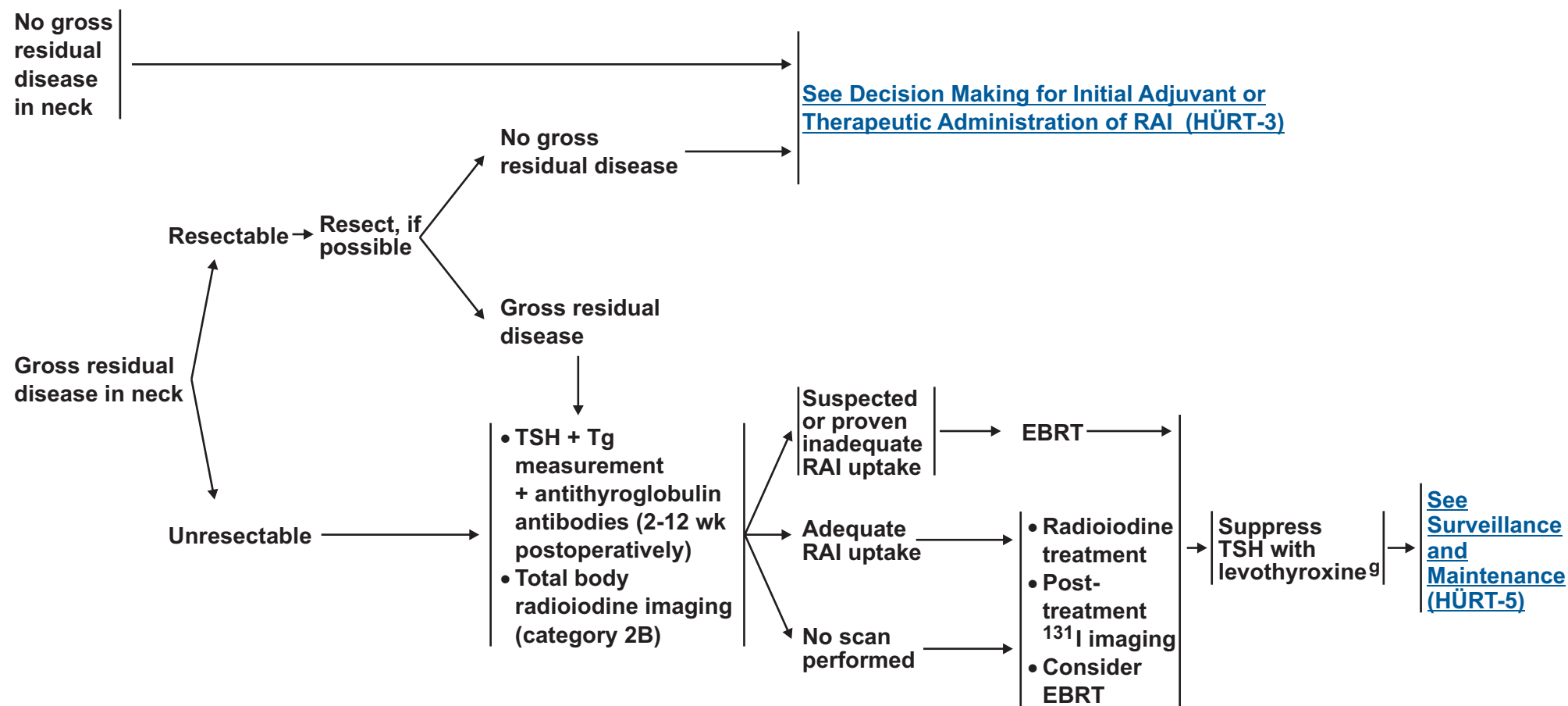
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CLINICO-PATHOLOGIC FACTORS

DECISION MAKING FOR INITIAL ADJUVANT OR THERAPEUTIC ADMINISTRATION OF RAI

RAI recommended (if any present):
- **Gross extrathyroidal extension**
- **Primary tumor > 4 cm**
- **Known or suspected distant metastases**
- **Extensive vascular invasion**

→ RAI therapy → **See FOLL-4**

RAI selectively recommended (if any present):[f]
- **Primary tumor 2-4 cm**
- **High-risk histology**
- **Minor vascular invasion**
- **Cervical lymph node metastases**
- **Minor extrathyroidal extension**
- **Multifocality**
- **Inappropriate postoperative Tg**

→ RAI or Further evaluation to determine need for RAI → **See FOLL-4**

→ Follow-up without RAI ablation → **See FOLL-5**

RAI not recommended (if all present):[f]
- **Follicular thyroid carcinoma**
- **Primary tumor < 2 cm**
- **Intrathyroidal**
- **No vascular invasion**
- **Appropriate postoperative Tg**
- **Clinical N0**
- **Clinical M0**

→ Follow-up without RAI ablation → **See FOLL-5**

[f]RAI ablation is not required for minimally invasive follicular thyroid carcinoma or Hürthle cell carcinoma confined to the thyroid when the primary tumor is small and demonstrates only invasion of the tumor capsule without vascular invasion. However, RAI ablation is recommended when the combination of individual clinical factors (such as the size of primary tumor, histology, degree of vascular invasion and/or lymph node metastases, post-operative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.
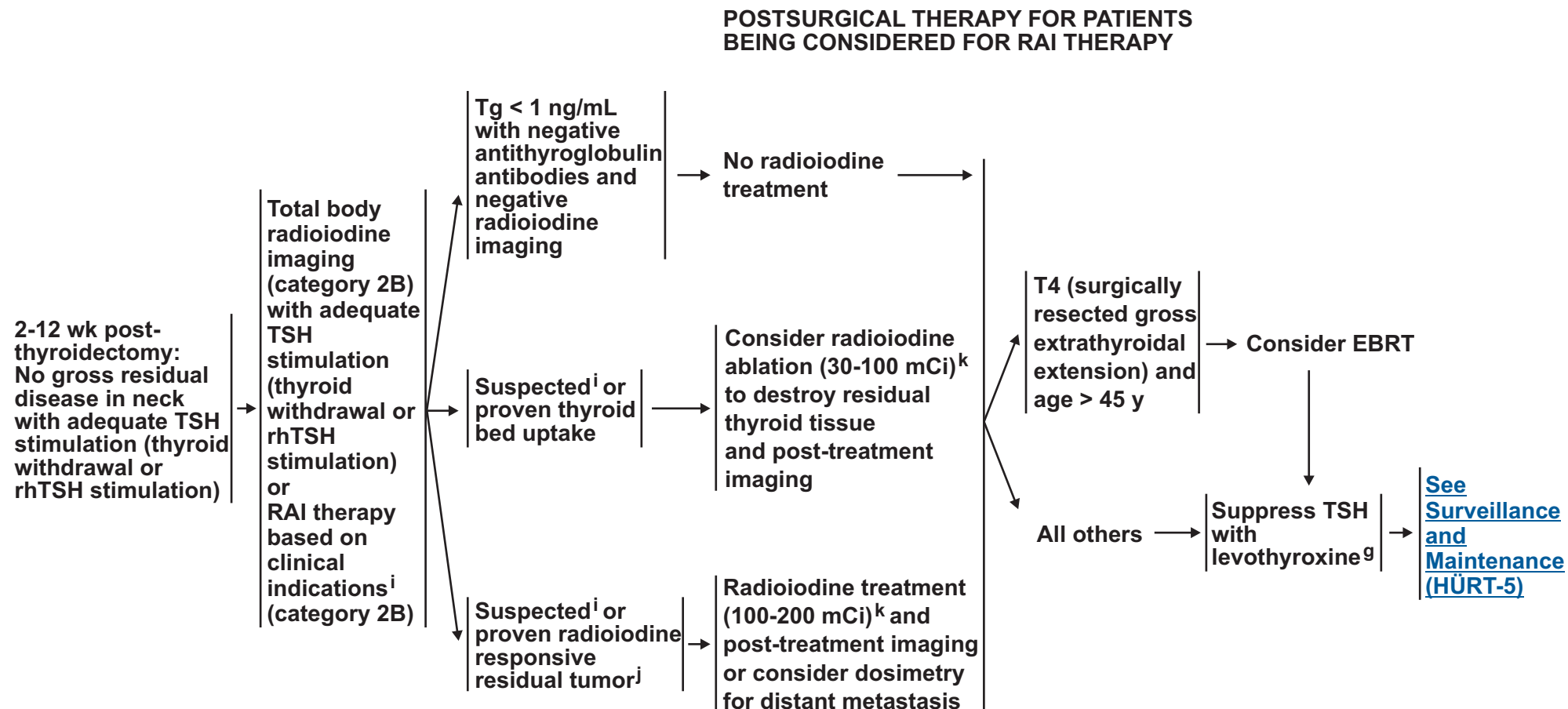
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**POSTSURGICAL THERAPY FOR PATIENTS
BEING CONSIDERED FOR RAI THERAPY**

2-12 wk post-thyroidectomy: No gross residual disease in neck with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) →

Total body radioiodine imaging (category 2B) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) or RAI therapy based on clinical indication[h] (category 2B) →

Tg < 1 ng/mL with negative antithyroglobulin antibodies and negative radioiodine imaging → **No radioiodine treatment** →

Suspected[f] or proven thyroid bed uptake → **Consider radioiodine ablation (30-100 mCi)[i] to destroy residual thyroid tissue and post-treatment imaging** →

Suspected[f] or proven radioiodine responsive residual tumor[h] → **Radioiodine treatment (100-200 mCi)[i] and post-treatment imaging or consider dosimetry for distant metastasis** →

Suppress TSH with levothyroxine[e] → **See Surveillance and Maintenance (FOLL-5)**

---

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

[f]Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

[h]All patients should be examined, and palpable neck metastases or sonographically significant disease should be surgically resected if possible before radioiodine treatment.

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

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SURVEILLANCE AND MAINTENANCE

- **Physical examination, TSH and Tg measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free**
- **Periodic neck ultrasound[j]**
- **Consider TSH stimulated Tg measurement in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[k]**
- **Consider TSH-stimulated radioiodine 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**
- **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)[l]**
- **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, chest CT, FDG-PET/CT)**
- **Patients treated with I-131 ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative Tg 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 as clinically appropriate, may be considered if clinical suggestion of recurrent disease.**

RECURRENT DISEASE

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

→ **Suppress TSH with levothyroxine[e]**

Locoregional recurrence →
**Surgery (preferred) if resectable[m] and/or
Radioiodine treatment,[i] if radioiodine imaging positive and/or
RT, if radioiodine imaging negative**

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

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

Metastatic disease → **See Treatment of Metastases (FOLL-6)**

---

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

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

[j]A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

[k]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. With a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).

[l]If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.

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

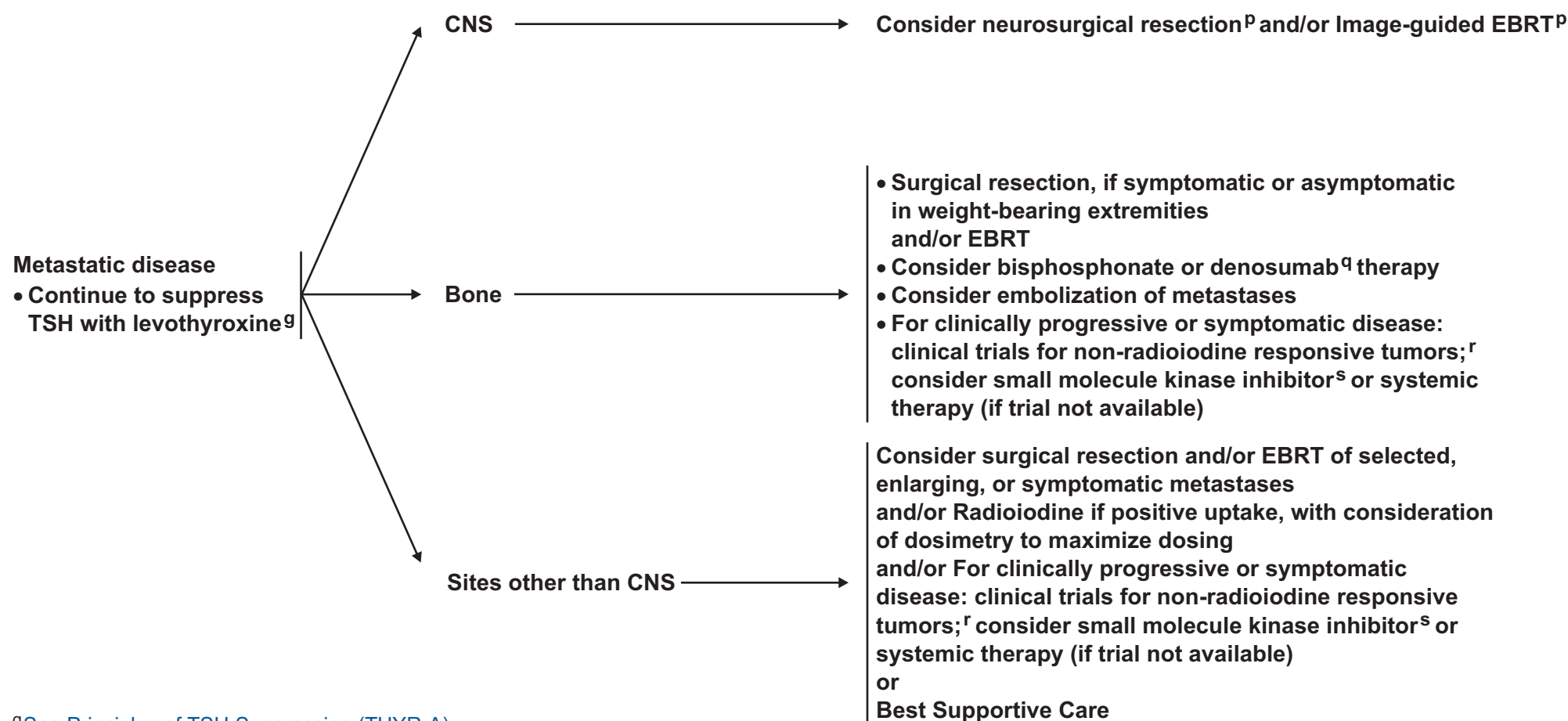**Note: All recommendations are category 2A unless otherwise indicated.**
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TREATMENT OF METASTASES

Metastatic disease
- **Continue to suppress TSH with levothyroxine[e]**

CNS ⟶ Consider neurosurgical resection[n] and/or Image-guided EBRT[n]

Bone ⟶
- Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities
  and/or Radioiodine treatment, if radioiodine imaging positive with consideration of dosimetry to maximize dosing
  and/or EBRT
- Consider bisphosphonate or denosumab[o] therapy
- Consider embolization of metastases
- For clinically progressive or symptomatic disease: clinical trials for nonradioiodine responsive tumors;[p] consider small molecule kinase inhibitor[q] or systemic therapy (if trial not available)

Sites other than CNS ⟶
Consider surgical resection and/or EBRT of selected, enlarging, or symptomatic metastases
and/or Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing
and/or For clinically progressive or symptomatic disease: clinical trials for non-radioiodine responsive tumors;[p] consider small molecule kinase inhibitor[q] or systemic therapy (if trial not available)
or
Best Supportive Care

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

[n] For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred. (See NCCN Guidelines for Central Nervous System Cancers)

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

[p] Cytotoxic chemotherapy has shown to have minimal efficacy. Clinical trials investigating novel targeted therapies are ongoing.
   See Clinical trials available at the NCCN member institutions.

[q] While not FDA approved for treatment of thyroid cancer, commercially available small molecule kinase inhibitors (such as sorafenib, sunitinib, or pazopanib [category 2B for pazopanib]) can be considered if clinical trials are not available or appropriate.

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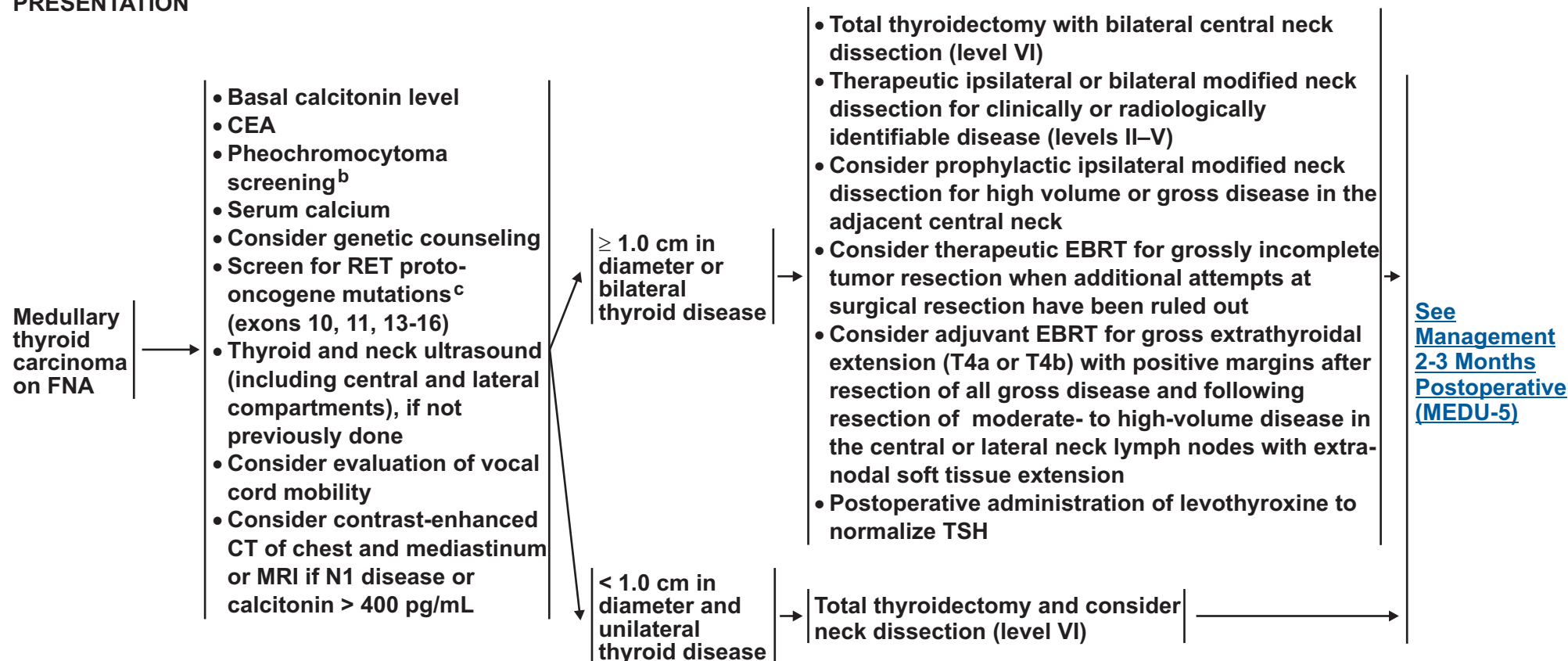**National Comprehensive Cancer Network®**

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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 for fixed, bulky, or substernal lesions[b]**
- **Consider evaluation of vocal cord mobility**
- **Consider chest x-ray**

Total thyroidectomy, if invasive cancer, metastatic disease or patient preference

If lymph node(s) positive perform therapeutic[c] dissection of affected compartment:
- **Central neck dissection (level VI)**
- **Lateral neck dissection (levels II, III, IV, and Vb, include levels I and Va if clinically involved). Consider preservation of the cervical sensory nerves**

If node(s) negative, consider prophylactic central neck dissection (category 2B)[d]

or

Lobectomy/isthmusectomy

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

→ Hürthle cell carcinoma[e] → See Postsurgical Evaluation (HÜRT-2)

Invasive cancer (extensive vascular invasion) → Completion of thyroidectomy →

Minimally invasive cancer[f] → Completion of thyroidectomy or Observe →

Benign → Observe

→ Consider levothyroxine therapy to keep TSH low or normal[g]

→ See Surveillance and Maintenance (HÜRT-5)

[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 will delay treatment with RAI but is required for optimal cervical imaging using CT.
[c] Ultrasound detected or clinically apparent disease.
[d] Possible benefit to reduce recurrence must be balanced with risk of hypoparathyroidism.
[e] Also known as oxyphilic, oncocytic, or follicular carcinoma, oncocytic type.
[f] Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.
[g] See Principles of TSH Suppression (THYR-A).

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POSTSURGICAL EVALUATION

g See Principles of TSH Suppression (THYR-A).
h Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

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CLINICO-PATHOLOGIC FACTORS

DECISION MAKING FOR INITIAL ADJUVANT OR THERAPEUTIC ADMINISTRATION OF RAI

RAI recommended (if any present):
- **Gross extrathyroidal extension**
- **Primary tumor > 4 cm**
- **Known or suspected distant metastases**
- **Extensive vascular invasion**

→ **RAI therapy** → **See HÜRT-4**

RAI selectively recommended (if any present): [h]
- **Primary tumor 2-4 cm**
- **High-risk histology**
- **Minor vascular invasion**
- **Cervical lymph node metastases**
- **Minor extrathyroidal extension**
- **Multifocality**
- **Inappropriate postoperative Tg**

→ **RAI or Further evaluation to determine need for RAI** → **See HÜRT-4**

→ **Follow-up without RAI ablation** → **See HÜRT-5**

RAI not recommended (if all present): [h]
- **Hürthle Cell Carcinoma**
- **Primary tumor < 2 cm**
- **Intrathyroidal**
- **No vascular invasion**
- **Appropriate postoperative Tg**
- **Clinical N0**
- **Clinical M0**

→ **Follow-up without RAI ablation** → **See HÜRT-5**

[h]RAI ablation is not required for minimally invasive follicular thyroid carcinoma or Hürthle cell carcinoma confined to the thyroid when the primary tumor is small and demonstrates only invasion of the tumor capsule without vascular invasion. However, RAI ablation is recommended when the combination of individual clinical factors (such as the size of primary tumor, histology, degree of vascular invasion, and/or lymph node metastases, postoperative thyroglobulin, and age at diagnosis) predicts a significant risk of recurrence, distant metastases, or disease-specific mortality.

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**POSTSURGICAL THERAPY FOR PATIENTS
BEING CONSIDERED FOR RAI THERAPY**

2-12 wk post-thyroidectomy: No gross residual disease in neck with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) →

Total body radioiodine imaging (category 2B) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) or RAI therapy based on clinical indications[i] (category 2B) →

- **Tg < 1 ng/mL with negative antithyroglobulin antibodies and negative radioiodine imaging** → **No radioiodine treatment** →
- **Suspected[i] or proven thyroid bed uptake** → **Consider radioiodine ablation (30-100 mCi)[k] to destroy residual thyroid tissue and post-treatment imaging**
- **Suspected[i] or proven radioiodine responsive residual tumor[j]** → **Radioiodine treatment (100-200 mCi)[k] and post-treatment imaging or consider dosimetry for distant metastasis**

→ **T4 (surgically resected gross extrathyroidal extension) and age > 45 y** → **Consider EBRT**

→ **All others** → **Suppress TSH with levothyroxine[g]**

→ **See Surveillance and Maintenance (HÜRT-5)**

---

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

[i]Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

[j]All patients should be examined, and palpable neck metastases or sonographically significant disease should be surgically resected if possible before radioiodine treatment.

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

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and Tg measurement + anti-thyroglobulin antibodies at 6 and 12 mo, then annually if disease free
- Periodic neck ultrasound[l]
- Consider TSH stimulated Tg measurement in patients previously treated with RAI and with negative TSH-suppressed Tg and anti-thyroglobulin antibodies[m]
- Consider TSH-stimulated radioiodine 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
- 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)[n]
- 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, chest CT, FDG-PET/CT)
- Patients treated with I-131 ablation, with a negative ultrasound, stimulated Tg < 2ng/mL (with negative Tg 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 as clinically appropriate, may be considered if clinical suggestion of recurrent disease.

RECURRENT DISEASE

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

→ **Suppress TSH with levothyroxine[g]**

Locoregional recurrence →
Surgery (preferred) if resectable[o] and/or
Radioiodine treatment,[k] if radioiodine imaging positive and/or
EBRT, if radioiodine imaging negative

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

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

Metastatic disease → **See Treatment of Metastases (HÜRT-6)**

---

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

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

[l] A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.

[m] 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. With a positive stimulated Tg, the concomitant RAI imaging may help determine whether treatment with RAI is indicated (ie, RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease).

[n] If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.

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

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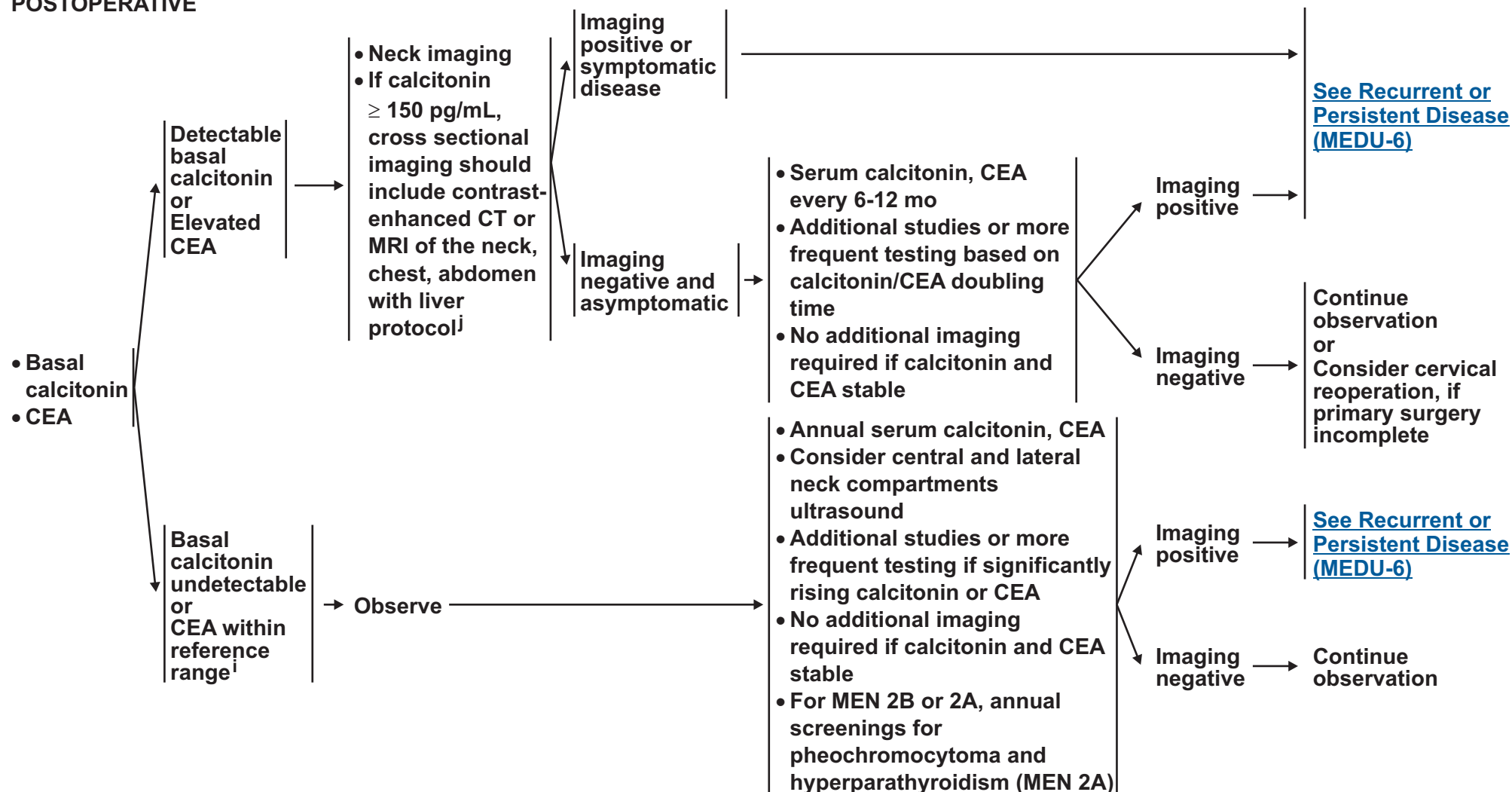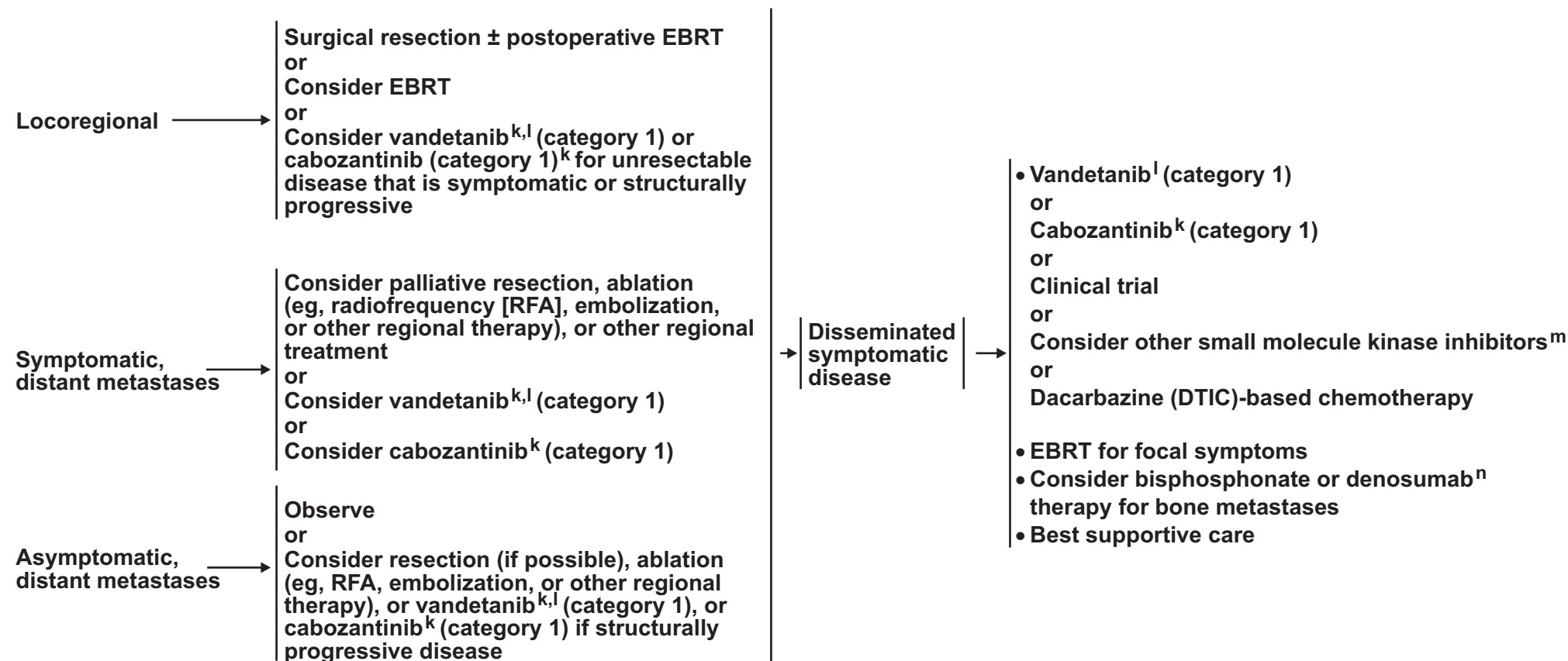
TREATMENT OF METASTASES

Metastatic disease
- **Continue to suppress TSH with levothyroxine[g]**

CNS → **Consider neurosurgical resection[p] and/or Image-guided EBRT[p]**

Bone →
- **Surgical resection, if symptomatic or asymptomatic in weight-bearing extremities and/or EBRT**
- **Consider bisphosphonate or denosumab[q] therapy**
- **Consider embolization of metastases**
- **For clinically progressive or symptomatic disease: clinical trials for non-radioiodine responsive tumors;[r] consider small molecule kinase inhibitor[s] or systemic therapy (if trial not available)**

Sites other than CNS →
Consider surgical resection and/or EBRT of selected, enlarging, or symptomatic metastases
and/or Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing
and/or For clinically progressive or symptomatic disease: clinical trials for non-radioiodine responsive tumors;[r] consider small molecule kinase inhibitor[s] or systemic therapy (if trial not available)
or
Best Supportive Care

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

[p] For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred. (See NCCN Guidelines for Central Nervous System Cancers)

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

[r] Cytotoxic chemotherapy has shown to have minimal efficacy. Clinical trials investigating novel targeted therapies are ongoing.
See Clinical trials available at the NCCN member institutions.

[s] While not FDA approved for treatment of thyroid cancer, commercially available small molecule kinase inhibitors (such as sorafenib, sunitinib, or pazopanib [category 2B for pazopanib]) can be considered if clinical trials are not available or appropriate.

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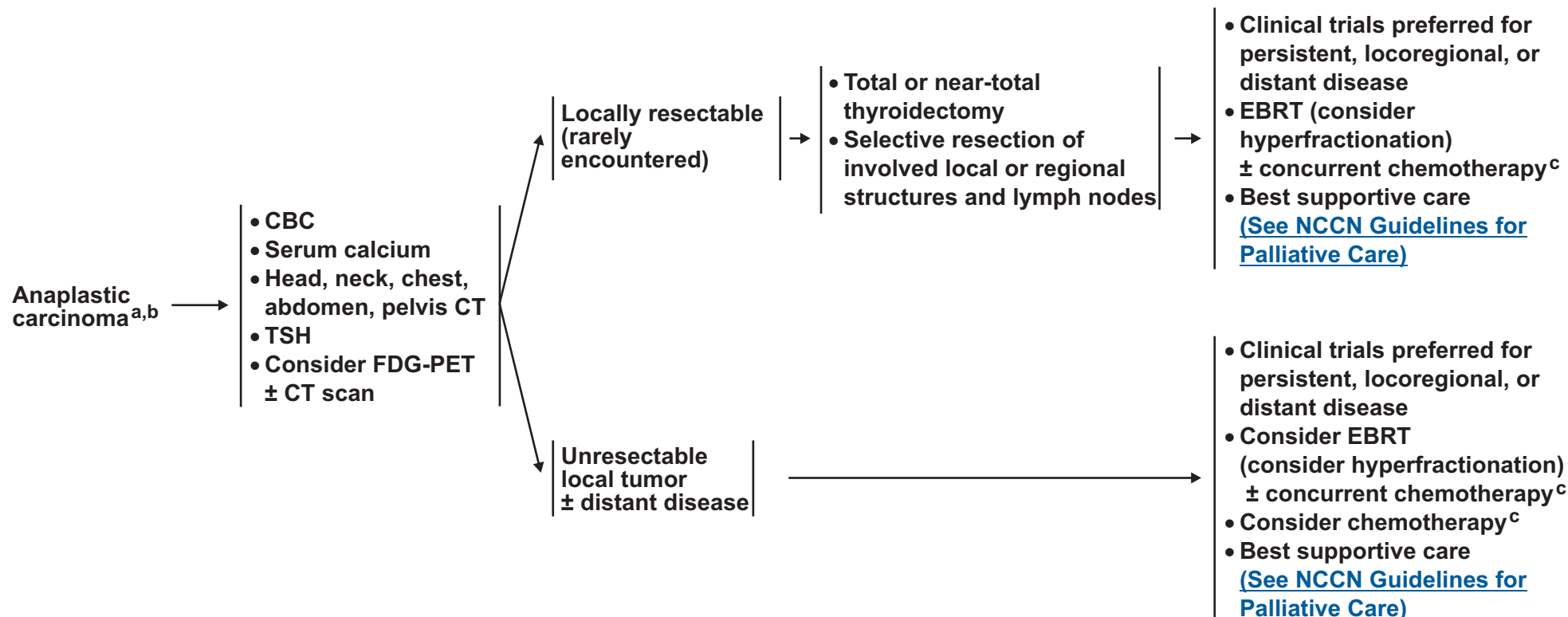
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CLINICAL PRESENTATION

ADDITIONAL WORKUP

PRIMARY TREATMENT

Medullary thyroid carcinoma on FNA

- Basal 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
- Consider contrast-enhanced CT of chest and mediastinum or MRI if N1 disease or calcitonin > 400 pg/mL

≥ 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 for grossly incomplete tumor resection when additional attempts at surgical resection have been ruled out
- Consider adjuvant EBRT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate- to high-volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension
- Postoperative administration of levothyroxine to normalize TSH

< 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,c]

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 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 Neuroendocrine Tumors Guidelines)

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CLINICAL PRESENTATION

ADDITIONAL WORKUP

MANAGEMENT

Medullary thyroid carcinoma diagnosed after initial thyroid surgery[d]

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

RET positive → See Additional Workup and Primary Treatment (MEDU-3)

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

[c]Germline mutation should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Neuroendocrine Tumors Guidelines)
[d]If initial thyroid surgery was less than a total thyroidectomy, additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) is generally unnecessary unless a positive RET mutation or radiographic evidence of disease (ie, biopsy-proven residual neck disease)

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CLINICAL PRESENTATION

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

ADDITIONAL WORKUP

PRIMARY TREATMENT

MEN 2B (codon 918, 883, or compound heterozygous [V804M + E805K, Y806C or S904C] RET mutations)

→

- Basal calcitonin level[f]
- CEA
- Pheochromocytoma screening[b,g]
- 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**
- **Consider adjuvant EBRT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate to high volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension (rarely recommended in children)**
- **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)[e]

→

- Basal calcitonin level[f]
- CEA
- Pheochromocytoma screening[b,g]
- 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 Neuroendocrine Tumors Guidelines)

[e] 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.).

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

[g] 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.

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PRIMARY TREATMENT

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

No primary hyperparathyroidism →

- Total thyroidectomy by age 5[a,e] or when mutation identified[a] (if mutation identified at older age)
- Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin[h] 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
- Consider adjuvant EBRT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate to high volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension (rarely recommended in children)
- 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 Neuroendocrine Tumors Guidelines)

[e] 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.).

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

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**MANAGEMENT
2-3 MONTHS
POSTOPERATIVE**

SURVEILLANCE

- **Basal calcitonin**
- **CEA**

Detectable basal calcitonin or Elevated CEA

→

- **Neck imaging**
- **If calcitonin ≥ 150 pg/mL, cross sectional imaging should include contrast-enhanced CT or MRI of the neck, chest, abdomen with liver protocol[j]**

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

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**

Imaging positive → **See Recurrent or Persistent Disease (MEDU-6)**

Imaging negative → **Continue observation or Consider cervical reoperation, if primary surgery incomplete**

Basal calcitonin undetectable or CEA within reference range[i]

→ **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 screenings for pheochromocytoma and hyperparathyroidism (MEN 2A)**

Imaging positive → **See Recurrent or Persistent Disease (MEDU-6)**

Imaging negative → **Continue observation**

[i]The likelihood of significant residual disease with an undetectable basal calcitonin is very low.
[j]Bone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.

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RECURRENT OR PERSISTENT DISEASE

Locoregional →
- **Surgical resection ± postoperative EBRT
or
Consider EBRT
or
Consider vandetanib^{k,l} (category 1) or cabozantinib (category 1)^k for unresectable disease that is symptomatic or structurally progressive**

Symptomatic, distant metastases →
- **Consider palliative resection, ablation (eg, radiofrequency [RFA], embolization, or other regional therapy), or other regional treatment
or
Consider vandetanib^{k,l} (category 1)
or
Consider cabozantinib^k (category 1)**

Asymptomatic, distant metastases →
- **Observe
or
Consider resection (if possible), ablation (eg, RFA, embolization, or other regional therapy), or vandetanib^{k,l} (category 1), or cabozantinib^k (category 1) if structurally progressive disease**

→ **Disseminated symptomatic disease** →

- **Vandetanib^l (category 1)
 or
 Cabozantinib^k (category 1)
 or
 Clinical trial
 or
 Consider other small molecule kinase inhibitors^m
 or
 Dacarbazine (DTIC)-based chemotherapy**

- **EBRT for focal symptoms**
- **Consider bisphosphonate or denosumab^n therapy for bone metastases**
- **Best supportive care**

^{k}Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.

^{l}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.

^{m}While not FDA approved for treatment of thyroid cancer, other commercially available small molecule kinase inhibitors (such as sorafenib or sunitinib) can be considered if clinical trials, vandetanib or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib.

^{n}Denosumab can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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FNA OR CORE BIOPSY FINDING

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT

Anaplastic carcinoma[a,b] →

- CBC
- Serum calcium
- Head, neck, chest, abdomen, pelvis CT
- TSH
- Consider FDG-PET ± CT scan

Locally resectable (rarely encountered) →
- Total or near-total thyroidectomy
- Selective resection of involved local or regional structures and lymph nodes

→
- Clinical trials preferred for persistent, locoregional, or distant disease
- EBRT (consider hyperfractionation) ± concurrent chemotherapy[c]
- Best supportive care (See NCCN Guidelines for Palliative Care)

Unresectable local tumor ± distant disease →
- Clinical trials preferred for persistent, locoregional, or distant disease
- Consider EBRT (consider hyperfractionation) ± concurrent chemotherapy[c]
- Consider chemotherapy[c]
- Best supportive care (See NCCN Guidelines for Palliative Care)

[a]An FNA diagnosis suspicious for anaplastic thyroid carcinoma should consider core biopsy.
[b]Consider multidisciplinary evaluation and referral to high-volume center with experience in treating this disease.
[c]See Systemic Therapy For Anaplastic Thyroid Carcinoma (ANAP-A).

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SYSTEMIC THERAPY FOR ANAPLASTIC THYROID CARCINOMA

Concurrent Chemoradiation Regimens[1]
- **Paclitaxel/Carboplatin**
- **Paclitaxel**
- **Cisplatin**
- **Doxorubicin**

Chemotherapy Regimens[1]
- **Paclitaxel/Carboplatin**
- **Paclitaxel[2]**
- **Doxorubicin[3]**

[1]Smallridge RC, Ain KB, Asa SL, et al. American thyroid association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-1139.
[2]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.
[3]Shimaoka K, Schoenfeld DA, DeWys WD, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985;56:2155-2160.

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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

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.

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Overview

Epidemiology

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the U.S. population for 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 less than 1%.[7,8] It is estimated that approximately 60,220 new cases of thyroid carcinoma will be diagnosed in the United States in 2013.[9] As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men. With the incidence increasing every year,[10] thyroid carcinoma is currently the fifth most common malignancy diagnosed in women.[9] Among persons aged 15 to 24 years, thyroid carcinoma accounts for 7.5% to 10% of all diagnosed malignancies.[11-13] 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 around age 49 years.[7,8]

The main histologic types of thyroid carcinoma include: 1) differentiated (including papillary, follicular, and Hürthle); 2) medullary; and 3) anaplastic (aggressive undifferentiated tumor). Of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, 80% had papillary carcinoma, 11% had follicular carcinoma, 3% had Hürthle cell carcinoma, 4% had medullary carcinoma, and 2% had anaplastic thyroid carcinoma.[14] The 10-year relative survival rates for patients with papillary, follicular, and Hürthle cell carcinomas were 93%, 85%, and 76%, respectively.[14]

In 2013, it is estimated that approximately 1850 cancer deaths will occur among persons with thyroid carcinoma in the United States.[15] Anaplastic thyroid 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. Although thyroid carcinoma occurs more often in women, mortality rates are lower for younger women.[7,8,16-18] The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004, but mortality rates decreased more than 44%.[8] From 1975 to 2004, thyroid cancer rates doubled in the United States.[19] Because overall mortality has remained stable since 1975, the increasing incidence may reflect earlier detection of subclinical disease (ie, small papillary cancers).[19,20] However, recent data show the incidence has increased by varying degrees across all tumor sizes.[21-24] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[15,25]

Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, Hürthle) thyroid carcinoma can be a challenge, because very few prospective randomized trials of treatment have been done.[26,27] Results from ongoing randomized trials will not be available for many years, given the typically prolonged course and relative infrequency of these tumors. Most of the information about treatment comes from studies of large patient cohorts in which 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.[28] The treatment of choice is surgery, whenever possible, followed by radioiodine (131I) in selected patients and thyroxine therapy in most patients. External-beam radiation therapy (EBRT) and chemotherapy have less prominent roles in managing these tumors.

Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma and usually causes papillary carcinoma. The thyroid glands of children are especially vulnerable to ionizing radiation. A child's thyroid gland has one of the highest risks of developing cancer of any organ. The thyroid gland is the only organ linked to risk at about 0.10 Gy.[5] The risk of radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma.[29] This suggests 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.[30] After the Chernobyl nuclear reactor accident in 1986, many children and adolescents developed papillary thyroid carcinoma (PTC) after being exposed to 131I fallout.[31] It became evident that 131I and other short-lived 131Is were potent thyroid carcinogens in these children, particularly those younger than 10 years when they were exposed.[32] Iodine deficiency increases the risk for radiation-induced thyroid cancer.[33] Although radiation-induced PTC

tends to appear more aggressive histologically and to have high recurrence rates, the prognosis for survival is similar to that of spontaneously occurring tumors.[34-36] Iodine deficiency is associated with follicular and anaplastic thyroid carcinomas.

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, Hürthle) 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.[1,37,38] 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.[1,37] 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.[18]

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 central neck; all nodules (even incidentalomas) should have this assessment; there is no size cutoff.[3,39,40] Note that some NCCN Panel Members do not feel it is necessary to do an ultrasound of the lateral neck at this point, hence the category 2B recommendation (see box at the beginning of this Discussion for the explanation of the different categories). A category 2B recommendation means that many (>50%), but not all (<85%), of

the NCCN Panel Members agree with the recommendation; the level of evidence (eg, phase II trial) is the same as for a category 2A recommendation. 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 Thyroid Carcinoma algorithm).[38,41]

FNA is the procedure of choice for evaluating suspicious thyroid nodules.[3,38,42] Recent data show that higher TSH levels are associated with an increased risk for differentiated thyroid carcinoma in patients with thyroid nodules.[43,44] FNA should be considered in patients with normal or elevated TSH, certain ultrasound features, and clinical findings. FNA of 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 Thyroid Carcinoma algorithm (see *Sonographic Features* in the section on *Nodule Evaluation*). 131I imaging is recommended in patients with low TSH.

Thyroid nodules smaller than 1 cm occur with such frequency in the asymptomatic general population that they are often found by serendipity when performing imaging studies for other head or neck problems. Often termed *incidentalomas,* nodules smaller than 1 cm are typically clinically insignificant lesions and usually do not require FNA, unless there are suspicious findings (see *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm).[4,39,45,46] However, it may be appropriate to evaluate patients with high-risk clinical features (eg, radiation exposure, history of thyroid cancer, multiple first-degree relatives with thyroid cancer), which are described later in this section.[3] In selected cases, it may be reasonable to follow these nodules with serial ultrasounds.

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 Thyroid Carcinoma algorithm).[3,41,47] The NCCN recommendations describe which nodules require further assessment with FNA and which can be observed. The ATA recently updated its guidelines on the management of thyroid nodules and thyroid cancer; its comprehensive guidelines also discuss ultrasound and FNA.[3] 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).[38,41] The Society of Radiologists in Ultrasound wrote a consensus statement in 2005 about management of thyroid nodules identified at thyroid ultrasonography. Their 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.[47] Suspicious criteria by ultrasound include increased central hypervascularity, hypoechoic mass, microcalcifications, infiltrative margins, and other features (see *Sonographic Features* in the section on *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm).

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 Thyroid Carcinoma algorithm).[48] 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 if symptoms of invasion into neck structures are present.[48,49] 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.[49] A patient's age and gender also affect the probability of malignancy. The risk of malignancy is higher in patients younger than 15 years, older than 45 years, and in those who are male. 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 thyroid carcinoma (MTC) 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.[3,50]

Some clinicians, especially in Europe,[51] recommend obtaining serum calcitonin levels from all patients with thyroid nodules to assess for MTC. 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.[3] A recent study showed that calcitonin screening may be cost effective in the United States.[52] 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.[53]

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) follicular lesion of undetermined significance; 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 Thyroid Carcinoma algorithm). These diagnostic categories for FNA results reflect the NCI's state of the science conference held in 2007.[38,41] 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 PTC —false-negative results are sometimes obtained; therefore, a reassuring FNA should not override worrisome clinical findings.[54]

Molecular diagnostics to detect individual mutations (eg, BRAF, 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.[55-62] For the 2013 update, the NCCN Panel added recommendations to consider molecular diagnostics for evaluating FNA results that are suspicious for 1) follicular or Hürthle cell neoplasms; or 2) follicular lesion of undetermined significance (see *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm).[63,64] Rather than proceeding to immediate surgical resection to obtain a definitive diagnosis in these categories, patients can be followed with observation if the application of a specific molecular diagnostic test 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 categories. Furthermore, in the cytologically indeterminate groups, the risk of malignancy for FNA can vary widely between institutions.[65-68] 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.[64,69]

Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of MTC.[41] Hürthle cell neoplasms can sometimes mimic MTC cytologically and on frozen section. Sometimes it can be difficult to discriminate between anaplastic thyroid carcinoma and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[70] Metastatic renal carcinoma can mimic a follicular neoplasm, melanoma can mimic MTC, and metastatic lung cancer can mimic anaplastic thyroid carcinoma.[41]

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens, such as those from the College of American Pathologists (CAP). The CAP protocol information and checklists—which were updated in June 2012 and reflect the 2010 staging (7th edition) from the AJCC—can be accessed at: (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Thyroid_12protocol_3002.pdf).

Follicular and Hürthle cell carcinomas are rarely diagnosed on FNA, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion.[28,71] Nodules that yield

an abundance of follicular cells with little or no colloid are nearly impossible to categorize as benign or malignant on the basis of FNA. Approximately 20% of these lesions are malignant.[48] Male gender, older patient age, and larger nodule size may increase the likelihood of a malignant diagnosis at surgery as high as 80%, whereas female gender, younger age, and smaller nodule size may reduce the risk as low as 5%. Repeat FNA will not resolve the diagnostic dilemma. However, molecular diagnostic testing may be useful (see *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm).

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.[3,72] Clinically euthyroid patients 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 "cold" or warm nodule and with suspicious clinical and sonographic features should proceed to surgery (see *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm).[2,3] Those patients with a high 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 should be considered for bilateral disease, unilateral disease greater than 4 cm (especially in men), 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 Thyroid Carcinoma algorithm).[48] Data suggest that ultrasound-guided FNA may be useful in diagnosing thyroid carcinoma, especially when repeating an FNA for a previously nondiagnostic biopsy.[3,73] In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.[74] Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of growth.[48] 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.[18] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[75,76] 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.[18] Distant metastases were the sites of recurrence in 21% of this patient cohort, most often (63%) in the lungs alone. Of the patients with distant metastases, 50% died of cancer.[18] However, 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 thyroglobulin [Tg] assays, high-resolution neck ultrasound) appear to have resulted in earlier detection of disease recurrence, which is now often found in the first 2 to 5 years of follow-up. These non-palpable small-volume lymph node recurrences often show little evidence of disease progression over many years and do not appear to be associated in an increase in mortality.[77,78]

Prognosis

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular thyroid carcinomas, patient age at the time of initial therapy and tumor stage are important.[18,79-81] Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in men. Thyroid carcinoma is more lethal in patients older than 40 years, increasingly so with each subsequent decade of life. The mortality rate increases dramatically after age 60 years (see Figure 1). 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.[18,79-82] 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

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survival is good.[83,84] 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.[85] 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.[86-88] 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.[18,83,89,90] Prognosis is less favorable in men than in women, but the difference is usually small.[18,88] 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.[18] Because of this risk factor, men with thyroid carcinoma—especially those who are older than 40 years—may be regarded with special concern.[91]

Familial Syndromes
Familial, non-MTC accounts for about 5% of PTCs and, in some cases, may be clinically more aggressive than the sporadic form.[92,93] For patients to be considered as having familial PTC, most studies require at least 3 first-degree relatives to be diagnosed with PTC because the finding of cancer in a single first-degree relative may just be a chance event. Microscopic familial PTC tends to be multifocal and bilateral, often with vascular invasion, lymph node metastases, and high rates of recurrence and distant metastases.[94] Other familial syndromes associated with PTC are familial adenomatous polyposis,[95] Carney complex (multiple neoplasia and lentiginosis syndrome, which affects endocrine glands),[96] and Cowden's syndrome (multiple hamartomas).[97] The prognosis for patients with all of these syndromes is not different from the prognosis of those with spontaneously occurring PTC.

Tumor Variables Affecting Prognosis
Some tumor features have a profound influence on prognosis.[82,98-100] The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, BRAF mutation status, and metastases.[101,102] For example, vascular invasion (even within the thyroid gland) is associated with more aggressive disease and with a higher incidence of recurrence.[3,103-106] The CAP protocol provides definitions of vascular invasion and other terms (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Thyroid_12protocol_3002.pdf). In patients with sporadic MTC, a somatic RET oncogene mutation confers an adverse prognosis.[107]

Histology
Although survival rates with typical PTC 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.[28,108] Follicular-variant PTC (FVPTC), which is recognized by its follicular architecture and typical papillary cytology, does not appear to have a worse prognosis than the pure papillary lesions if the FVPTC is encapsulated.[82,108-110] Molecular diagnostic testing is also useful for diagnosing FVPTC.[58]

Follicular thyroid carcinoma is typically a solitary encapsulated tumor that may be more aggressive than PTC. 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.[111] 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.[112] FNA or frozen section study cannot differentiate a minimally invasive follicular thyroid carcinoma from a follicular adenoma.[38,71] Therefore, the tumor is often simply referred to as a *follicular neoplasm* by the cytopathologist (see *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm). The diagnosis of follicular thyroid carcinoma is assigned only after diagnostic lobectomy or thyroidectomy and indeed only after analysis of the "permanent" histologic sections 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.[82] The poor prognosis is closely related to older age at the time of diagnosis, advanced tumor stage, and larger tumor size.[18] The mortality for papillary and follicular thyroid carcinomas is 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.[18,113]

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.[114,115] Molecular studies suggest, however, that this tumor may be more similar to papillary than follicular thyroid carcinomas.[116,117] Benign and malignant Hürthle 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.[118] 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.[119,120] 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.[121,122] Fewer Hürthle cell carcinomas concentrate 131I than do papillary or follicular carcinomas. 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.[123] In the National Cancer Data Base report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.[14]

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.[124] The risk of recurrence in papillary microcarcinomas ranges from 1% to 2% in unifocal papillary microcarcinomas, to 4% to 6% in multifocal papillary microcarcinomas.[125,126] 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,[127] which may be the presenting feature and also may be associated with distant metastases.[124] Otherwise, small (<1.5 cm)

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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; 30-year cancer-specific mortality is 0.4% compared to 7% (*P* < .001) for tumors 1.5 cm or larger.[18] In fact, the prognosis for papillary and follicular thyroid carcinomas is incrementally poorer as tumors increase in size.[113,128] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas (see Figure 2).[18]

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 thyroid carcinomas.[18,129] 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.[18,130]

Lymph Node Metastases
In one review, nodal metastases were found in 36% of 8029 adults with PTC, in 17% of 1540 patients with follicular thyroid carcinoma, and in up to 80% of children with papillary carcinoma.[82] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[131] 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).[132] Older patients (>45 years) with PTC and lymph node metastases also have decreased survival.[133] A recent review by Randolph et al emphasized the correlation between the size and

number of metastatic lymph nodes and the risk of recurrence.[134] 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 thyroid carcinomas. Almost 10% of patients with papillary carcinoma and up to 25% of those with follicular thyroid carcinoma develop distant metastases. About 50% of these metastases are present at the time of diagnosis.[82] Distant metastases occur even more often in patients with Hürthle cell cancer (35%) and in those patients diagnosed after age 40 years.[121,123] 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, whether the metastases concentrate 131I, and morphology on chest radiograph.[121,123,135,136]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[82] Even so, some pulmonary metastases are compatible with long-term survival. 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.[137] The survival rates are highest in young patients with diffuse lung metastases seen only on 131I imaging and not on x-ray.[136-138] Prognosis is worse with large pulmonary metastases that do not concentrate 131I.[121,123,135]

Tumor Staging

The NCCN Guidelines for Thyroid Carcinoma do not use TNM stages as the primary determinant of management. Instead, many tumor and patient characteristics play important roles in these NCCN Guidelines. Many specialists in thyroid cancer also follow this paradigm. When treating differentiated thyroid carcinoma, where most patients do not die, many clinicians place a stronger emphasis on potential morbidity than on mortality (see *Surgical Complications* in this Discussion). Staging was revised in the 2002 guidelines (6th edition) from the AJCC for patients with papillary and follicular thyroid carcinomas who are older than 45 years.[139] Note that the AJCC considers Hürthle cell carcinoma as a variant of follicular carcinoma, as does the WHO. Revised staging guidelines from the AJCC (7th edition) became effective January 1, 2010 (see Table 1).[114] In the 7th edition, TI has been divided into TIa and TIb. These changes include using the term *moderately advanced* instead of *resectable* and the term *very advanced* instead of *unresectable.* Many studies (including those described in this Discussion) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[140] and not the 6th or 7th editions.[114,139]

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.[80,86,114,139,141] 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 low- and high-risk patients.[128] 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 decreased from 99% to 89% and 56%, and 24%, respectively.[86]

Unfortunately, a study that classified 269 patients with PTC according to 5 different prognostic paradigms found that some patients in the lowest risk group from each approach died of cancer.[89] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[139,142] The AJCC TNM staging approach (see Table 1), 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,[143,144] 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 are young. Two studies have shown the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.[80,145]

A three-tiered staging system (low, intermediate, high) that uses clinico-pathologic features to risk stratify with regard to the risk of recurrence has recently been suggested and validated.[3,146-149] 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. More recently, 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.[150] 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 (ie, ipsilateral lobectomy vs. total thyroidectomy) is very controversial for lower-risk PTC, 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. Circumstances in which lobectomy is not recommended are detailed in the NCCN Guidelines. This debate reflects the limitations of prognostic scoring[88] and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Patients treated at the Mayo Clinic 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.[151]

Cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy were assessed in patients with PTC considered to be low risk by AMES criteria.[152] 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 and colleagues concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk PTC.[152]

Most NCCN Panel Members (and guidelines from the ATA) recommend total thyroidectomy for all patients in whom the diagnosis of PTC is assigned preoperatively,[3,28,153] because such procedures are associated with improved disease-free survival, even in children and adults with low-risk tumors.[75,90,152,154] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe.[82,151] After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and 131I therapy)[18] and the highest frequency (11%) of subsequent pulmonary metastases.[155] However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.[34] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for total thyroidectomy.[18]

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 thyroid carcinoma based on 1) the low mortality among those patients categorized as low risk by the AMES and other prognostic classification schemes (ie, most patients); and 2) the high complication rates reported with more extensive thyroidectomy.[87,141,156] The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole-body 131I imaging.

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 Papillary Carcinoma algorithm).[18,124,157] Total lobectomy alone is also adequate

treatment for minimally invasive follicular thyroid carcinomas (see *Primary Treatment* in the NCCN Follicular [Thyroid] Carcinoma algorithm). However, completion thyroidectomy is recommended for any of the following: tumor more than 4 cm, positive margins, gross extrathyroidal extension, macroscopic multifocal disease, confirmed 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 (eg, strap muscles, trachea, larynx, vasculature, esophagus, recurrent laryngeal nerve).[101,158,159]

Completion Thyroidectomy

This procedure is recommended when remnant ablation is anticipated or if long-term follow-up (with serum Tg determinations with [or without] whole-body 131I imaging) is planned. Large thyroid remnants are difficult to ablate with 131I.[155] 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.[129,160-166] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[163]

Miccoli and colleagues 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.[90] 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.[164]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults[167] and children[90,168] 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.[169] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[170] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[171]

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.[172] Recently, minimally invasive surgical procedures (eg, robotic surgery) have been used for thyroidectomy. Although fewer postoperative complications are reported with robotic surgery, long-term oncologic outcome data are not yet available.[173,174]

Radioactive Iodine

Postoperative Radioiodine

The NCCN Panel recommends a selective use approach to postoperative radioactive iodine (RAI) remnant ablation. 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. Postoperative RAI is recommended for patients at high risk of having persistent disease remaining after total thyroidectomy and includes patients with gross extrathyroidal extension, a primary tumor greater than 4 cm, or known/suspected distant metastases (see *Clinco-Pathologic Factors* in the NCCN Papillary, Follicular, and Hürthle Cell Carcinoma algorithms).Postoperative RAI is also recommended for select patients who are at greater risk for recurrence based on clinical indications (eg, high-risk histology, vascular invasion, clinically significant cervical lymph node metastases, inappropriately elevated postoperative serum Tg).[3,175,176] However, the NCCN Panel does not routinely recommend RAI for patients with either unifocal or multifocal papillary microcarcinomas (<1 cm) confined to the thyroid. 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.[3,177]

Studies show decreased recurrence and disease-specific mortality for higher-risk populations when postoperative 131I therapy is administered as part of the initial treatment.[18,81,89,178,179] 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.[178] Some found that remnant ablation had less of a therapeutic effect, perhaps, because more extensive locoregional surgery had been done.[128]

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.[180] Longer follow-up suggests that overall survival is not decreased or increased in these patients.[181] However, a recent study reported that the incidence of secondary malignancies (eg, leukemia, salivary gland malignancies) has increased in patients with low-risk thyroid cancer (ie, T1N0) who received RAI.[182] Debate continues about ablating the thyroid bed with 131I after total thyroidectomy.[3,128,178,183] In patients with PTC who were at low risk for recurrence, thyroid remnant ablation did not decrease recurrence rates.[157,176] A recent long-term study (n=1298) found that overall survival is not improved in patients who receive RAI ablation.[184]

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 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 low- and intermediate-risk patients, the clinical benefit of routine remnant ablation as a requirement for optimal follow-up remains uncertain. Recent data suggest that lower doses of RAI are as effective as higher doses (ie, 30 vs. 100 mCi) for ablation in patients with low-risk thyroid cancer (eg, T1b/T2 [1-4 cm], clinical N0 disease).[26,27] The NCCN Guidelines now reflect a more cautious approach to using RAI ablation based on these randomized trials.[185] If RAI ablation is used, the NCCN Guidelines now recommend (category 1) 30 mCi of 131I for RAI

ablation in low-risk patients based on these randomized trials. This same ablation dose (ie, 30 mCi) may be considered (category 2B) in slightly higher-risk patients (see *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Papillary, Follicular, and Hürthle Cell Carcinoma algorithms). RAI ablation is not recommended in very-low-risk patients.

Diagnostic Total Body Imaging and Thyroid Stunning

When indicated, diagnostic total body 131I imaging is recommended by many (>50%), but not all (<85%), of the NCCN Panel (category 2B) after surgery to assess the completeness of thyroidectomy and to assess whether residual disease is present (eg, see *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Papillary, Follicular, and Hürthle Cell Carcinoma algorithms). However, a phenomenon termed *stunning* may occur when imaging doses of 131I induce follicular cell damage.[186] Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent 131I.[187]

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 (of not more than 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.[186-188] 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.[186] 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.[3,186,189-191] 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. Note that diagnostic imaging is used less often for low-risk patients.

Administration of Radioiodine Therapy

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.[3,186,189,192,193] Most patients at NCCN centers receive RAI therapy 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 ambulatory patients.[192] 131I therapy with high doses (>200 mCi) is best done in medical centers with experience using high doses.

Fixed 131I 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 to 6475 MBq) of 131I. Cancer growing through the thyroid capsule (and incompletely resected) is treated with 150 to 200 mCi (5550 to 7400 MBq). Patients with distant metastases are usually treated with 200 mCi (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.[194,195] 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 remain in the whole body 48 hours after treatment. The administered activity of RAI therapy should be adjusted for pediatric patients.[3,196] A recent 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.[197]

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.[192] 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.[198] 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.[198]

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.[199] 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.[200,201]

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.[202] About 6% of patients with detectable serum Tg levels (which are less than 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.[203] rhTSH is well tolerated. Nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[201] It is associated with significantly fewer symptoms and

dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[203]

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.[201] Data showed that the combination of rhTSH–stimulated whole-body imaging and serum Tg measurements detected 100% of metastatic carcinoma.[201] 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.[201,204]

Measuring Serum Tg

Serum Tg measurement is the best means of detecting thyroid tissue (including carcinoma). Tg should 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.[200-202,205] Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or rhTSH stimulation. Serum Tg generally does not rise as high 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)[201] and an imaging time of 30 minutes or until 140,000 counts are obtained.

The sensitivity and specificity of various Tg assays, however, vary widely in different laboratories, even with the use of an international standard (CRM 457).[206,207] 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 is likely to 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.[207,208] These antibodies typically falsely lower the Tg value in immunochemiluminometric assays (ICMAs) and immunoradiometric assays (IRMA), while raising the value in older RAIs. 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.[208]

In one study, 49% of patients had a recurrence if they had undetectable serum Tg and serum anti-Tg antibody levels of 100 U/mL or more when compared with only 3% of patients with undetectable serum Tg and serum anti-Tg antibodies of less than 100 U/mL.[209] 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.[210]

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 (ie, diagnostic 131I imaging, neck ultrasonography, CT, MRI, PET). Pulmonary metastases may be found only after administering therapeutic doses of 131I and obtaining whole-body imaging within a few days of treatment.[211] 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 had not been detected after 2-mCi (74 MBq) diagnostic imaging.[212]

Unfortunately, most diagnostic imaging–negative/Tg-positive patients are not rendered disease free by 131I therapy; however, the tumor burden may be diminished.[213] 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 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.[3,189,214] However, the optimal serum levels of TSH have not been defined because of a lack of specific data; therefore, the NCCN Panel recommends tailoring

the degree of TSH suppression to the risk of recurrence and death from thyroid cancer for each individual patient. For patients with known residual carcinoma (or those at high risk for recurrence), the recommended TSH level is below 0.1 mU/L. For low-risk patients and for those patients with an excellent response to initial therapy (are in remission), the recommended TSH level is either slightly below or slightly above 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] An adequate daily intake of calcium (1200 mg/day) and vitamin D (1000 units/day) is recommended for patients whose TSH levels are chronically suppressed.

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma have been reported for patients treated with thyroid hormone suppressive therapy.[18,178,180,214-217] 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).[217] 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 high-risk patients but were achieved with modest suppression in stage II patients.[180] 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 EBRT.[218] One retrospective study reported a benefit of adjuvant EBRT after RAI in patients older than 40 years with invasive PTC (T4) and lymph node involvement (N1).[219] Local recurrence and locoregional and distant failure were significantly improved. A second study reported improved 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 PTC with microscopic residuum. Not all patients received RAI therapy.[81] Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of PTC. 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%).[220] 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%).[220] However, these patients had not received RAI. Similar benefit was shown with RAI alone in comparable patients treated with RAI after surgery.[220] Another study found that recurrences did not occur in high-risk patients 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.[221]

External-Beam RT and Surgical Excision of Metastases

Isolated skeletal metastases should be considered for surgical excision or external irradiation. 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.[222,223] 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.[224] Most recurrent tumors respond well to surgery, 131I therapy, or EBRT.[3,225]

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, 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.[226] In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.[227] Combination chemotherapy is not clearly superior to doxorubicin therapy alone.[82] Overall, traditional cytotoxic systemic chemotherapy (eg, doxorubicin) has minimal efficacy in patients with metastatic differentiated thyroid disease.[228]

Novel treatments for patients with metastatic differentiated thyroid carcinoma have been evaluated.[229-232] Agents that have been evaluated include: 1) multitargeted kinase inhibitors, such as motesanib diphosphate (AMG-706),[233,234] sorafenib,[235-240] sunitinib,[237,241-243] axitinib,[244] vandetanib,[245] pazopanib,[246] and lenvatinib;[247,248] 2) the histone deacetylase inhibitors, vorinostat and depsipeptide;[249,250] 3) the DNA methylation inhibitor, decitabine; 4) the heat-shock protein 90 (HSP-90) inhibitor, 17-allylamino-17-demethoxygeldanamycin (17-AAG); 5) the proteasome inhibitor, bortezomib;[251] 6) a selective cyclooxygenase-2 inhibitor, celecoxib;[252] and 7) a derivative of thalidomide, lenalidomide.[253,254]

Clinical trials suggest that tyrosine kinase inhibitors (TKIs) appear to have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of subjects, usually for about 12 to 24 months.[237,246,248,255-257] Vandetanib and cabozantinib, oral TKIs, are recommended for the treatment of MTC in patients with unresectable locally advanced or metastatic disease (see *Medullary Thyroid Carcinoma* in this Discussion and the NCCN algorithm).[258-261] 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.[262] Pazopanib has been reported to cause reversible hypopigmentation.[263]

Papillary Thyroid Carcinoma

Surgical Therapy

Imaging is recommended before surgery to ascertain the extent of disease and thus aid in the surgical decision-making process (eg, whether to do a total thyroidectomy vs. lobectomy plus isthmusectomy). A CT/MRI should be performed if the lesion is fixed, bulky, or substernal; iodinated contrast is required for optimal cervical imaging with CT. A thyroid and neck ultrasound (including central and lateral compartments) is recommended if not previously done.[264] In one report, cervical ultrasound performed before primary surgery for newly diagnosed disease identified metastatic sites not appreciated on physical examination in 20% of patients, and surgical strategy was altered in many patients.[265] Evaluation of vocal cord mobility can be considered. A chest x-ray can also be considered.

The NCCN Panel agreed on the characteristics of higher-risk patients who require total thyroidectomy and neck dissection as the primary treatment (see *Preoperative or Intraoperative Decision-Making Criteria* in the NCCN Papillary [Thyroid] Carcinoma algorithm).[3,266,267] A total thyroidectomy is recommended for patients with any one of the following factors, including: age younger than 15 years or older than 45 years, radiation history, known distant metastases, bilateral nodularity, extrathyroidal extension, tumor greater than 4 cm in diameter, cervical lymph node metastases, or aggressive variant. Note that *aggressive variant disease* is defined as tall cell variant, columnar cell, or poorly differentiated features. If lymph nodes are palpable or positive on biopsy, then central neck dissection (level VI) and lateral neck dissection (at least levels II–IV and Vb) are recommended.[268] If the nodes are negative, prophylactic central neck dissection (level VI) can be considered (category 2B) but is not required in all cases.[269-273]

The NCCN Panel did not agree about the preferred primary surgery for patients who are assumed to be at lower risk of cancer-specific mortality. The majority of Panel Members recommended (category 2B) total thyroidectomy in any patient in whom PTC was identified preoperatively or at the time of surgery. However, a minority of Panel Members recommended (category 2B) that, initially, lobectomy plus isthmusectomy is adequate surgery for properly selected patients at low risk of recurrence. Lobectomy plus isthmusectomy is recommended for patients who cannot (or refuse to) take thyroid hormone replacement therapy for the remainder of their lives.[274] 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.

A study in more than 5000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for both low- and high-risk patients.[275] 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

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undergo lobectomy or total thyroidectomy.[276] However, most guidelines (eg, NCCN, ATA) do not recommend observation for patients with PTC.[3] Another study in 2784 patients with differentiated thyroid carcinoma (86% with PTC) found that total thyroidectomy was associated with increased survival in high-risk patients.[180] A study in 52,173 patients found that total thyroidectomy improves survival in patients with PTC greater than 1 cm when compared with lobectomy.[277] For patients who undergo lobectomy plus isthmusectomy (lower-risk patients), completion of thyroidectomy is recommended for any one of the following risk factors: large tumor (>4 cm), positive margins, gross extrathyroidal extension, macroscopic multifocal disease, vascular invasion, or confirmed nodal metastases.

Incidentally discovered PTCs 1 to 4 cm in size may warrant a completion thyroidectomy (category 2B) for an aggressive variant (see *Primary Treatment* in the NCCN Papillary [Thyroid] Carcinoma algorithm); observation 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 *TSH Suppression* in the NCCN Thyroid Carcinoma algorithm). Lobectomy is sufficient for tumors resected with all of the following: negative 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 *TSH Suppression* in the NCCN Thyroid Carcinoma algorithm).

Radioactive Iodine

Therapy with 131I is recommended for patients with tumors found on examination, imaging studies, or by increased serum Tg levels if these tumors are unresectable and if they concentrate 131I. 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.[196] RAI is not recommended for patients with either unifocal or multifocal papillary microcarcinomas (<1 cm) confined to the thyroid, and clinical N0 and M0.[185] The NCCN Panel agrees that RAI treatment is not needed for patients with Tg levels less than 1 ng/mL, negative 131I imaging, and negative anti-Tg antibodies. 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 *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Papillary [Thyroid] Carcinoma algorithm).[3]

For unresectable locoregional recurrence, RAI treatment and EBRT are recommended if the 131I imaging is positive; EBRT alone is another option in the absence of 131I uptake.[278,279] When recurrent disease is suspected based on a high serum-stimulated Tg values (>10 ng/mL) and based on negative imaging studies (including PET scans), RAI therapy can be considered (category 3) using an empiric fixed dose of 100 to 150 mCi of 131I (see *Recurrent Disease* in the NCCN Papillary [Thyroid] Carcinoma algorithm). However, the NCCN Panel had a major disagreement about this recommendation (category 3), because some do not feel that these patients should receive RAI. 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

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study, no survival advantage was associated with empiric high-dose RAI in imaging-negative patients.[280] 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.[281,282] For patients with metastatic disease that is not locoregional, the NCCN Panel recommends individualized treatment based on the tumor location(s) (eg, CNS, bone, sites other than CNS) (see *Treatment of Metastases* in the NCCN Papillary [Thyroid] Carcinoma algorithm).

Adjuvant External-Beam RT

For patients with unresectable gross residual disease in the neck (suspected or proven) that does not concentrate RAI, EBRT is recommended.[3] EBRT can be considered for patients older than 45 years with macroscopic disease (ie, T4 [surgically resected gross extrathyroidal extension]) that does not concentrate RAI and without gross residual disease in their neck (see *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Papillary [Thyroid] Carcinoma algorithm).[3,278,283-286]

Surveillance and Maintenance

The recommendations for surveillance and maintenance are described in the algorithm (see *Surveillance and Maintenance* in the NCCN Papillary [Thyroid] Carcinoma algorithm).[3] In patients who have had total (or near total) thyroidectomy and thyroid remnant ablation, the ATA Guidelines define the absence of persistent tumor (ie, disease free) as: 1) absence of clinical evidence of tumor; 2) absence of imaging evidence of tumor; and 3) undetectable Tg levels (during TSH suppression) and absence of anti-Tg antibodies.[3] The NCCN Panel added a new recommendation for 2013 (see *Surveillance and Maintenance* in the NCCN Papillary [Thyroid] Carcinoma algorithm).

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 low-risk patients (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 Papillary [Thyroid] Carcinoma algorithm). Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.[3]

Recurrent and Metastatic 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). For unresectable locoregional recurrences, 131I therapy is recommended for tumors that concentrate 131I (ie, 131I imaging positive), and EBRT alone is recommended for those that do not concentrate 131I (ie, 131I imaging negative). Unresectable iodine-responsive locoregional disease may additionally be treated with EBRT to improve outcomes.

For metastatic disease, several therapeutic approaches are recommended (see *Treatment of Metastases* in the NCCN Papillary [Thyroid] Carcinoma algorithm), depending on the site and number of tumor foci.[3,287] Patients should continue to receive levothyroxine to suppress TSH levels. For skeletal metastases, surgical palliation is recommended for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are 131I treatment

(if the 131I imaging is positive) and/or EBRT.[288-290] 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.[291-293] Embolization of metastases can also be considered.[294]

For metastases to the CNS, neurosurgical resection should be considered for appropriate cases and/or image-guided EBRT (see *Treatment of Metastases* in the NCCN Papillary [Thyroid] Carcinoma algorithm). For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred (see the NCCN Guidelines for Central Nervous System).[222,223] For sites other than the CNS, surgical resection and/or EBRT can be considered for selected, enlarging, or symptomatic metastases; 131I is recommended if the tumor concentrates the radioisotope. For clinically progressive or symptomatic disease, recommended options include: 1) clinical trials for non-131I-responsive tumors; 2) consider small molecule kinase inhibitors or systemic therapy if a clinical trial is not available; or 3) best supportive care.[295] Because chemotherapy is usually not effective, the NCCN Guidelines recommend clinical trials for non-RAI avid tumors; small molecule kinase inhibitors (ie, sorafenib, sunitinib, pazopanib [category 2B for pazopanib]) or traditional cytotoxic systemic therapy can be considered if a trial is not available.[3,235,238,240,242,246,296-298] However, TKI therapy may be most appropriate for patients with unresectable, recurrent disease that is threatening vital structures or is not responsive to EBRT.[299] Of interest, hypothyroidism has been reported in some patients receiving sunitinib or sorafenib, but it also seems to be associated with increased progression-free survival (PFS).[300] Note that use of pazopanib is a category 2B recommendation, because some NCCN Panel Members do not feel it is appropriate to use. Several

agents are in clinical trials (http://clinicaltrials.gov/ct2/results?term=thyroid+cancer).

Follicular Thyroid Carcinoma

Because the diagnosis and treatment of papillary and follicular thyroid carcinoma are similar, 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. Thus, FNA is not specific for follicular thyroid carcinoma (unlike papillary carcinoma) and accounts for the main differences in management of the 2 tumor types. 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. Further diagnostic and treatment decisions for patients who present with follicular neoplasms are based on their TSH levels (see *Nodule Evaluation* in the NCCN Thyroid Carcinoma algorithm).

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

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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 a few foci of vascular invasion and often requires examination of at least 10 histologic sections.[301] These tumors may also be simply followed carefully, because minimally invasive follicular carcinomas 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 Follicular [Thyroid] Carcinoma algorithm).

The other features of management and follow-up for follicular thyroid carcinoma are identical to those of papillary carcinoma. Thus, RAI ablation to destroy residual thyroid tissue should be considered for suspected or proven thyroid bed uptake. 131I ablation and post-treatment imaging (with consideration of dosimetry for distant metastasis) is recommended for suspected or proven 131I-responsive residual tumor (see *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Follicular [Thyroid] Carcinoma algorithm). 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 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,[114,115] although the prognosis of Hürthle cell carcinoma is worse.[120,302,303] The Hürthle cell variant of PTC is rare and seems to have a prognosis similar to follicular carcinoma.[304] The management of Hürthle cell (oxyphilic) 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 positive nodes, or prophylactic (category 2B) central neck compartment dissection may be considered for negative nodes; and 2) metastatic Hürthle cell tumors are less likely to concentrate 131I.

Postoperative EBRT can be considered for advanced Hürthle cell lesions (ie, T4) in patients older than 45 years (see *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Hürthle Cell [Thyroid] Carcinoma algorithm), similar to the management for papillary carcinoma.[3] Nonetheless, 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 (category 3) 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 Hürthle Cell [Thyroid] Carcinoma algorithm).[120]

NCCN Panel Members do not all agree about the following recommendations, which are reflected in the category 2B decisions. Some NCCN Panel Members do not feel that diagnostic total body 131I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) should be recommended (category 2B) before 131I therapy is administered, because the thyroid remnant may interfere with the

scan.[3] Other Panel Members do not feel that patients with clinical indications for RAI (suspicion based on pathology, postoperative Tg, and intraoperative findings) require imaging (category 2B) (see *Postsurgical Therapy for Patients Being Considered for RAI Therapy* in the NCCN Hürthle Cell [Thyroid] Carcinoma algorithm).

Medullary Thyroid Carcinoma

MTC arises from the neuroendocrine parafollicular C cells of the thyroid.[305-307] 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; 2) MEN 2B; or 3) familial MTC.[308,309] Sporadic disease typically presents in the fifth or sixth decade. Familial forms of the disease tend to present at earlier ages.[305] The 10-year overall survival is about 75%.[14] 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.[310]

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.[311] However, 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 Medullary [Thyroid] Carcinoma algorithm) 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 Thyroid Carcinoma algorithm). 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.[312-314] 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.[315,316] 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.[306,307] 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[317] 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 Medullary [Thyroid] Carcinoma algorithm). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade, 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.[306,307,318] Familial MTC is now viewed as a variant of MEN 2A.[305] 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.[305] 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 is associated with poorer patient prognosis.

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.[319,320] Genetic testing for *RET* proto-oncogene mutations is recommended for all newly diagnosed patients with clinically apparent sporadic MTC, and for screening children and adults in known kindreds with inherited forms of MTC; genetic counseling should be considered. MTC can involve difficult ethical decisions for clinicians if parents or guardians refuse screening and/or treatment for children with possible MTC.[321]

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum carcinoembryonic antigen [CEA]) and screening 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 prospectively treat coexisting pheochromocytoma to avoid hypertensive crisis during surgery. Pheochromocytoma can be removed using laparoscopic adrenalectomy.[305,322] Preoperative thyroid and neck ultrasound (including central and lateral neck compartments) is recommended. Contrast-enhanced CT or MRI of the chest and mediastinum can be considered if the patient has N1 disease or calcitonin greater than 400 pg/mL.[305] Evaluation of vocal cord mobility can also be considered.

Staging

As previously mentioned, the NCCN Guidelines for Thyroid Carcinoma do not use TNM stages to guide therapy. Instead, many tumor and patient characteristics 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) (7th edition of the AJCC Cancer Staging Manual).[114] Staging for MTC slightly changed in the 2010 AJCC update (ie, 7th edition of the AJCC Cancer Staging Manual).[114] 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[140] and not to the 6th or 7th editions.[114,139] In one study with a median follow-up period of only 4 years, mortality from MTC was 0% for stage I, 13% for stage II, 56% for stage III, and 100% for stage IV disease.[323]

However, the TNM staging classification lacks other important prognostic factors.[324] 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.[310,324] 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.[325,326] 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.[326]

Other factors that may be important for predicting a worse prognosis include: 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor;[327] 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level;[328] and 3) postoperative residual hypercalcitoninemia.[323] 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.[324,329] Codon analysis is useful for predicting prognosis.[305,330] Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease.[331] 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).[332]

Surgical Management

Surgery is the main treatment for MTC, because no curative systemic therapy for MTC is available, although vandetanib and cabozantinib are recommended for locally advanced and metastatic MTC (see *Recurrent or Persistent Disease* in this Discussion).[258-261] 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.[305]

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 *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. 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 Medullary [Thyroid] Carcinoma algorithm).[266,310] 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

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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.[305,333] Note that C634 mutations are the most common mutation.[305] Total thyroidectomy is recommended in the first year of life or at diagnosis for MEN 2B patients with 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 Medullary [Thyroid] Carcinoma algorithm), because these *RET* mutations carry the highest risk for MTC (ie, level D).[305,334]

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.[305,334] 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 Medullary [Thyroid] Carcinoma algorithm).[305,335] Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.[305,336] 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.[337]

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.[305] 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 Medullary [Thyroid] Carcinoma algorithm).

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 Medullary [Thyroid] Carcinoma algorithm).

Adjuvant RT

EBRT has not been adequately studied as adjuvant therapy in MTC.[338] 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.[339] However, most centers do not have extensive experience with adjuvant EBRT for this

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disease. When EBRT is used, 40 Gy is typically administered in 20 fractions to the cervical, supraclavicular, and upper mediastinal lymph nodes over 4 weeks, with subsequent booster doses of 10 Gy in 5 fractions to the thyroid bed.[192] Postoperative adjuvant EBRT to the neck and mediastinum may be considered for patients with gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and after resection of moderate-volume to high-volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension; however, this is rarely recommended in children (see *Primary Treatment* in the NCCN Medullary [Thyroid] Carcinoma algorithm).[305] EBRT can also be given to palliate painful or progressing bone metastases.[290,305]

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 Medullary [Thyroid] Carcinoma algorithm).

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.[340] 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.[323,341] 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.[342] 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.[343,344] 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.[344]

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 Medullary [Thyroid] Carcinoma algorithm). For patients with a detectable basal calcitonin or elevated CEA level, neck imaging is recommended. Patients with undetectable calcitonin 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 or MRI of the neck, chest, and abdomen with a liver protocol. Bone scan and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.[305] 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.[305]

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 asymptomatic patients with abnormal markers and repeated negative imaging, continued observation or consideration of cervical re-operation 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

Vandetanib and cabozantinib are oral receptor TKIs that increased PFS in patients with metastatic MTC.[260,345-348] Vandetanib is a multitargeted TKI; it inhibits RET, vascular endothelial growth factor (VEGFR), and endothelial growth factor receptor (EGFR).[259] In a phase III randomized trial in unresectable, locally advanced, or metastatic MTC (n = 331), vandetanib increased PFS when compared with placebo (hazard ratio [HR], 0.46; 95% CI, 0.31–0.69; *P* < .001); overall survival data are not yet available.[346,349] 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 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022405s003lbl.pdf). However, access is restricted through a vandetanib Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity (see boxed warning in the prescribing information). The NCCN Panel recommends vandetanib (category 1) for patients with recurrent or persistent MTC (see *Recurrent or Persistent Disease* in the NCCN Medullary [Thyroid] Carcinoma algorithm). For the 2013 update, the NCCN Panel revised the recommendation for vandetanib from category 2A to category 1, because the phase III randomized trial was published.[259]

Cabozantinib is a multitargeted TKI that inhibits RET, VEGFR2, and MET. In a recent phase III 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.[260] The FDA recently approved the use of cabozantinib for

patients with progressive, metastatic MTC (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203756lbl.pdf).[260,261] For the 2013 update, the NCCN Panel now recommends cabozantinib (category 1) based on the phase III randomized trial and FDA approval (see *Recurrent or Persistent Disease* in the NCCN Medullary [Thyroid] Carcinoma algorithm). 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. For unresectable locoregional disease that is symptomatic or structurally progressive, the following treatment can be considered: 1) EBRT; 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 Medullary [Thyroid] Carcinoma algorithm). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but observation is acceptable given the lack of data regarding alteration in outcome.

In the setting of disseminated symptomatic metastases, the NCCN Panel recommends the following: 1) vandetanib (category 1);[259,347,348] 2) cabozantinib (category 1);[260] 3) clinical trial; or 4) consider other small molecule kinase inhibitors (ie, sorafenib or sunitinib) if clinical trials, vandetanib, or cabozantinib are not available or appropriate.[350-355] If the patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered, using dacarbazine or combinations including dacarbazine.[356,357] EBRT can be used for focal symptoms.

Bisphosphonate therapy or denosumab can be considered for bone metastases.[291-293] Best supportive care is also recommended.

In patients with metastatic MTC, sorafenib reduces symptoms due to hypercalcitonemia and metastases.[353] Recently, stable disease rates of about 50% and clinical benefit rates of approximately 70% have been seen with motesanib diphosphate (AMG-706).[347,358] In addition, clinical response was seen in 6 of 8 patients with MTC who were treated with a combination of sorafenib and the farnesyltransferase inhibitor, tipifarnib.[359] Sunitinib was associated with clinical response in several case reports.[354,360,361] Clinical trials are assessing the effectiveness of novel multitargeted therapies including sunitinib,[243,350,354] sorafenib,[359,362] and pazopanib. Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.[262] Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.

Novel therapies and the management of aggressive MTC have been reviewed.[230,363-365] 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.[347] A recent phase II trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with 131I.[366] Overall survival was improved in the subset of patients with increased calcitonin doubling times.[367]

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[368] Patients with anaplastic carcinoma are older than those with differentiated

carcinomas, with a mean age at diagnosis of approximately 71 years.[369] Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[79,369] The incidence of anaplastic thyroid carcinoma is decreasing.[368] As previously mentioned, anaplastic carcinoma is the least common type of thyroid carcinoma. Of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, only 2% had anaplastic thyroid carcinoma.[14]

Approximately 50% of patients with anaplastic thyroid carcinoma 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.[370] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, 131I imaging cannot be used and RAI treatment is not effective in these patients with anaplastic thyroid carcinoma.

Patients with anaplastic thyroid carcinoma present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[301,371] 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. All anaplastic thyroid carcinomas are considered stage IV (A, B, or C) (see Table 1). The T4 category includes: 1) T4a tumors that are intrathyroidal and surgically resectable; and 2) T4b tumors that are extrathyroidal and not surgically resectable. However, clinically apparent anaplastic tumors are usually unresectable.

The diagnosis of anaplastic thyroid carcinoma is usually established by core or surgical biopsy. Sometimes it is difficult to discriminate between anaplastic thyroid carcinoma and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[70,372] Diagnostic procedures include a CBC, serum calcium, TSH level, and imaging studies. CT scans of the neck can accurately determine the extent of the thyroid tumor and identify tumor invasion of the great vessels and upper aerodigestive tract structures.[373] FDG-PET scans with (or without) CT scans can be considered. Bone metastases are usually lytic.

Prognosis

No effective therapy exists for anaplastic thyroid carcinoma; it is almost uniformly fatal.[374] The median survival from diagnosis is about 5 months.[372,375] The 1-year survival rate is about 20%.[371,375] 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. 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.[376] Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, WBC ≥10,000 mm^3, and dyspnea as a presenting symptom.[377,378]

Treatment

Once the diagnosis of anaplastic thyroid carcinoma is confirmed, it is essential to rapidly determine whether local resection is an option.[368] However, most patients with anaplastic thyroid carcinoma have unresectable or metastatic disease. The patency of the airway should be considered throughout the patient's course. 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.[375,376,379,380] EBRT can increase short-term survival in some patients; EBRT can also improve local control and can also be used for palliation (eg, to prevent asphyxiation).[338,368,372,378,381,382]

Treatment with single-drug chemotherapy is not very effective, although some patients may respond or have stable disease.[372] Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year. Distant metastases then become the leading cause of death.[383] 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.[384,385] IMRT may be useful to reduce toxicity.[338,372,386-390] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival.

For 2013, the NCCN Panel added systemic therapy recommendations (see *Systemic Therapy for Anaplastic Thyroid Carcinoma* in the NCCN Anaplastic [Thyroid] Carcinoma algorithm).[372,391] 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.[372] 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 anaplastic thyroid carcinoma.[372] Paclitaxel (single agent) may benefit

some newly diagnosed patients; increased survival has been reported in stage IVB patients.[392-394] 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.[372,394]

Given the poor outcome with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials. Clinical trials include fosbretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crinobulin (EPC2407), which are vascular disrupting agents), CS-7107 (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib (http://clinicaltrials.gov/ct2/results?term=thyroid+cancer).[235,254,296,391,395-401]

A patient with anaplastic thyroid carcinoma had a durable complete response in a phase I trial with CA4P, and was disease free for several years.[402,403] A study in 26 patients with advanced anaplastic thyroid carcinoma showed that 33% of patients survived more than 6 months after receiving fosbretabulin.[400] A larger trial in 80 patients (FACT) reported that the addition of fosbretabulin—to a carboplatin/paclitaxel regimen—increased median survival (8.2 vs. 4.0 months), although the trial was not powered to detect a difference.[391] Multimodality therapy is recommended in patients with locally resectable disease (see *Primary Treatment* in the NCCN Anaplastic [Thyroid] Carcinoma algorithm).[372,386,391,404-408] 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.[409]

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NCCN Guidelines Version 2.2013
Thyroid Carcinoma

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Discussion

Figures 1 and 2

Figure 1:

Relationship of cancer recurrence and mortality to patient age at time of diagnosis
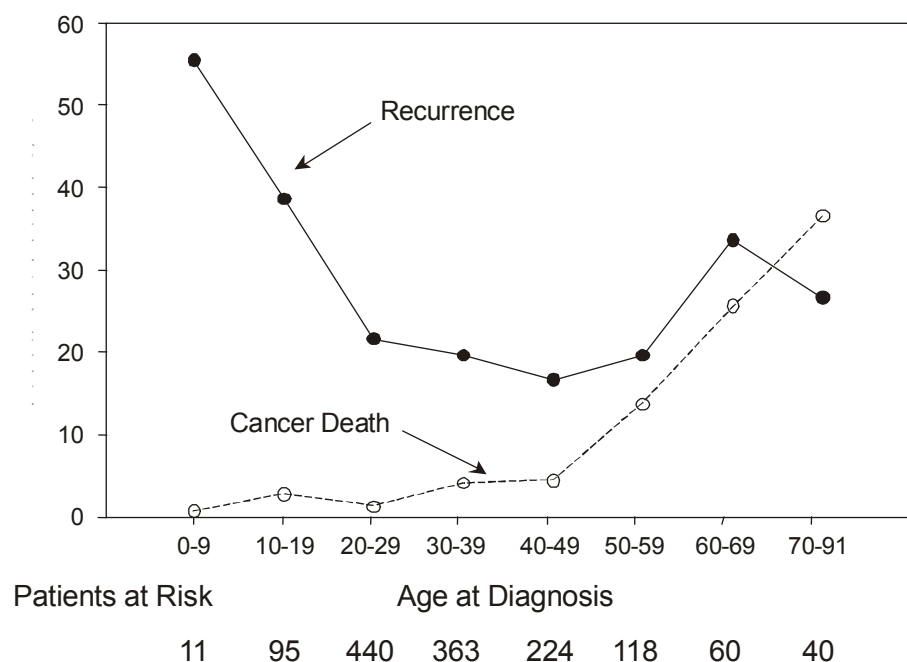
Recurrence

Cancer Death

Patients at Risk — Age at Diagnosis

0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-91
11	95	440	363	224	118	60	40

(Reprinted and adapted from AM J Med, 97, Mazzaferri EL and Jhiang SM, Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer, pp 418-428, 1994, with permission from Excerpta Medica Inc.).

Figure 2:

Relationship of cancer recurrence and mortality to tumor size
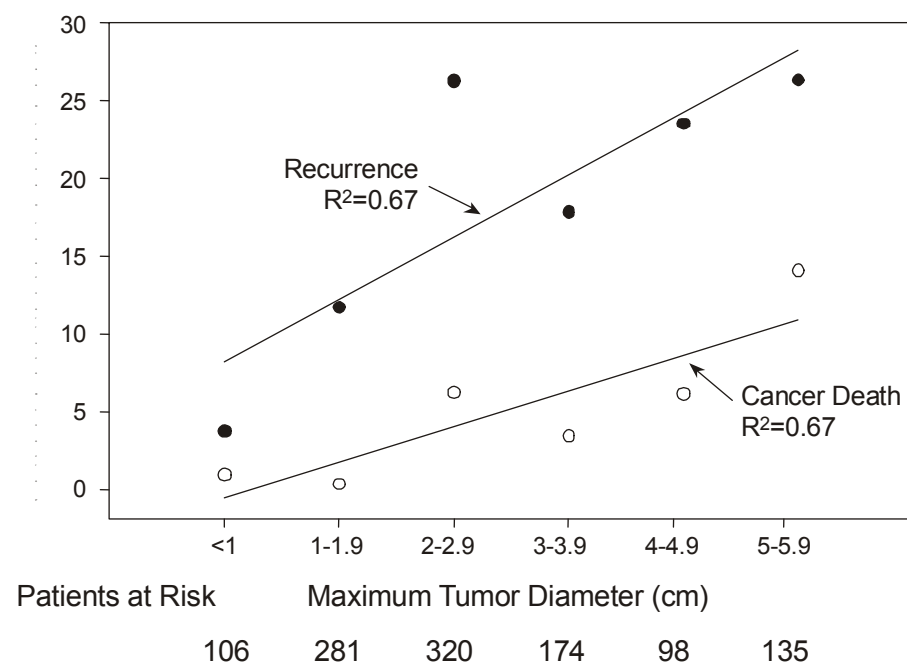
Recurrence
$R^2=0.67$

Cancer Death
$R^2=0.67$

Patients at Risk — Maximum Tumor Diameter (cm)

<1	1-1.9	2-2.9	3-3.9	4-4.9	5-5.9
106	281	320	174	98	135

(Reprinted and adapted from AM J Med, 97, Mazzaferri EL and Jhiang SM, Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer, pp 418-428, 1994, with permission from Excerpta Medica Inc.).

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