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NCCN Clinical Practice Guidelines in Oncology™

Thyroid Carcinoma

V.1.2007

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This manuscript is being updated to correspond with the newly updated algorithm.

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 Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Summary of Guidelines Updates

Summary of the Guidelines updates

Summary of changes in the 1.2007 version of the Thyroid Carcinoma Guidelines from the 1.2006 version include:

Thyroid Nodule Evaluation:

- Footnote "a" was added to solitary nodule > 1 cm. In selected cases, it may be reasonable to follow with serial ultrasounds (THYR-1).
- Incidentally identified focal PET positive lesion in the thyroid was added to the "Increased suspicion" category (THYR-1).
- Hürthle cell was further categorized as "well-differentiated" or "poorly differentiated" (THYR-2).
- The category of benign was clarified as "Hürthle cells in the absence of neoplasm" and the recommendation to repeat FNA or consider surgery was added if nodule growth (THYR-2).

Papillary Carcinoma:

- Footnote "a" stating that age is an approximation and not an absolute determinant was added to the page (PAP-1).
- Aggressive variant was added to the preoperative or intraoperative decision-making criteria (PAP-1).
- If patient initially treated with lobectomy, "extrathyroidal extension" was added as an indication for completion thyroidectomy (PAP-1).

Papillary Carcinoma, Follicular Carcinoma, and Hürthle Cell Carcinoma:

- Tumor and disease characteristics were added to distinguish surveillance from postsurgical therapy (PAP-3), (FOLL-2), (HÜRT-2)
- The categories guiding the recommendations for postsurgical therapy were revised. The new categories are "Suspected or proven thyroid bed uptake" and "Suspected or proven radioiodine avid residual tumor" (PAP-4), (FOLL-3), (HÜRT-3)
- The Surveillance and Maintenance section was revised (PAP-5), (FOLL-4), (HÜRT-4):
  - ➤ Bullet 3: The recommendation for TSH stimulated thyroglobulin was modified to "without radioiodine scan at 12 mo" in patients "previously treated with RAI" with recent negative neck ultrasound and "undetectable" TSH suppressed thyroglobulin "(anti-thyroglobulin antibody negative) and T1-2, N0-1, M0 at initial staging".
  - ➤ Bullet 4: The recommendation for radioiodine scan was reworded, If detectable thyroglobulin, distant metastases or soft tissue invasion on initial staging, radioiodine scan every 12 mo until "no radioactive iodine avid tumor is evident" (either withdrawal of thyroid hormone or rhTSH).
- Patients with metastatic disease of other extracervical sites, the footnote "Cytotoxic chemotherapy has been shown to have minimal efficacy. Clinical trials are investigating novel targeted therapies. See Clinical trials available at the NCCN member institutions." was added (PAP-6), (FOLL-5), (HÜRT-5).

Medullary Carcinoma:

- Footnote "b" regarding testing for exon 8 is new to the page. A contrast-enhanced CT of the chest and mediastinum and abdomen was added to the workup section (MEDU-1).
- Treatment recommendations are based on the measurement of parathyroid hormone and not the elevation of calcitonin or CEA (MEDU-3).
- For patients with an elevated or positive calcitonin or CEA, a contrast-enhanced CT or MRI was added of the neck chest and abdomen with liver protocol (MEDU-4).
- The recommendation for additional studies during surveillance was clarified with the modifier "if significantly rising calcitonin or CEA" (MEDU-4).
- The recommendation for ablation in recurrent or persistent disease was clarified as "radiofrequency, embolization, or other regional therapy" (MEDU-5).

Anaplastic Carcinoma:

- The CT recommendation was expanded to include head, chest, abdomen, and pelvis (ANAP-1).
- The qualifier of "rarely encountered" was added to locally resectable disease.
- The treatment recommendation of airway management ± tracheostomy was removed for unresectable disease (ANAP-1).

Nodule Evaluation

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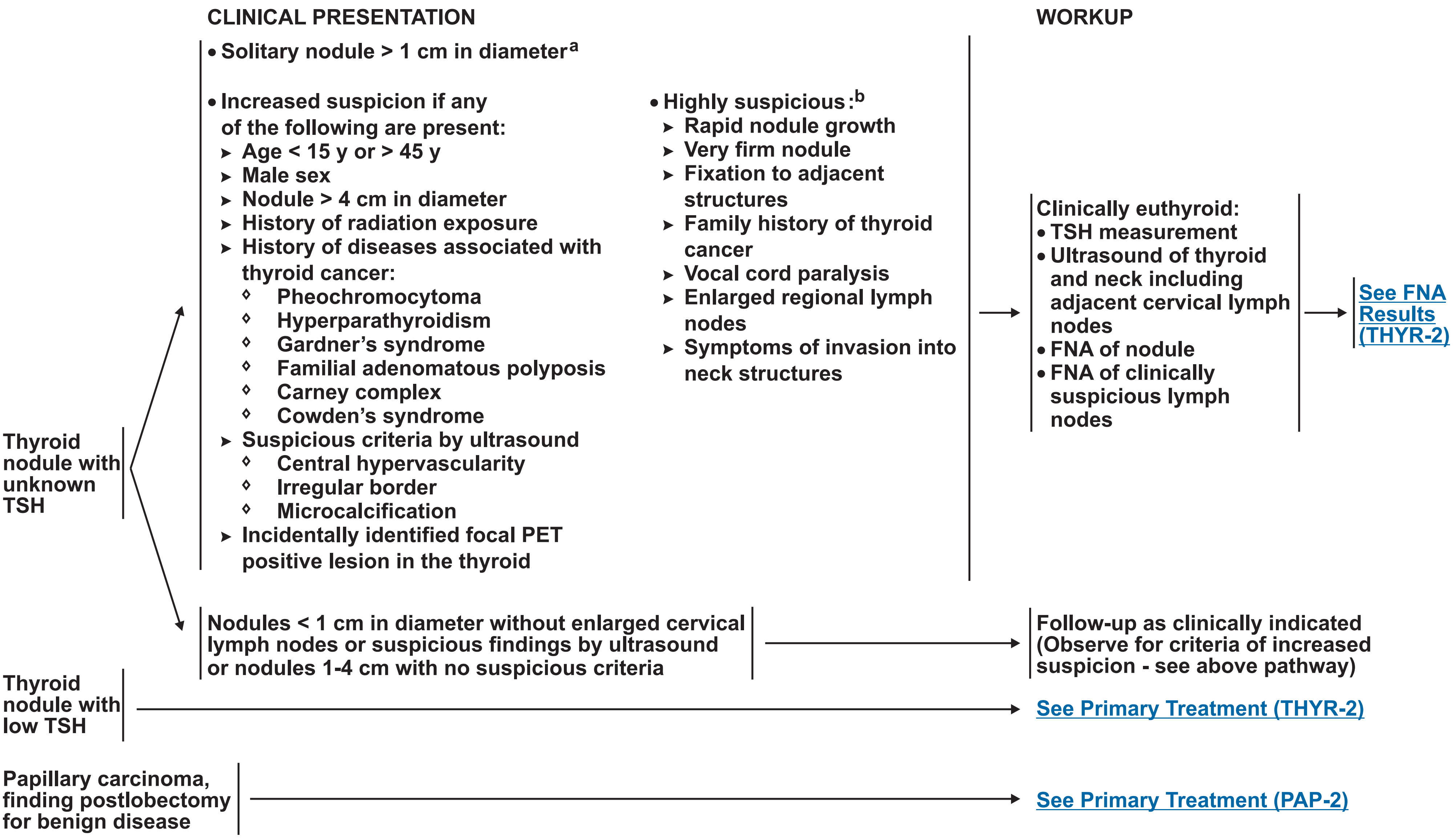

CLINICAL PRESENTATION

WORKUP

Thyroid nodule with unknown TSH

- Solitary nodule > 1 cm in diameter[a]
- Increased suspicion if any of the following are present:
  - Age < 15 y or > 45 y
  - Male sex
  - Nodule > 4 cm in diameter
  - History of radiation exposure
  - History of diseases associated with thyroid cancer:
    - Pheochromocytoma
    - Hyperparathyroidism
    - Gardner's syndrome
    - Familial adenomatous polyposis
    - Carney complex
    - Cowden's syndrome
  - Suspicious criteria by ultrasound
    - Central hypervascularity
    - Irregular border
    - Microcalcification
  - Incidentally identified focal PET positive lesion in the thyroid
- Highly suspicious:[b]
  - Rapid nodule growth
  - Very firm nodule
  - Fixation to adjacent structures
  - Family history of thyroid cancer
  - Vocal cord paralysis
  - Enlarged regional lymph nodes
  - Symptoms of invasion into neck structures

→ Clinically euthyroid:
- TSH measurement
- Ultrasound of thyroid and neck including adjacent cervical lymph nodes
- FNA of nodule
- FNA of clinically suspicious lymph nodes

→ See FNA Results (THYR-2)

Nodules < 1 cm in diameter without enlarged cervical lymph nodes or suspicious findings by ultrasound or nodules 1-4 cm with no suspicious criteria → Follow-up as clinically indicated (Observe for criteria of increased suspicion - see above pathway)

Thyroid nodule with low TSH → See Primary Treatment (THYR-2)

Papillary carcinoma, finding postlobectomy for benign disease → See Primary Treatment (PAP-2)

[a] In selected cases, it may be reasonable to follow with serial ultrasounds.

[b] Consider surgery after FNA.

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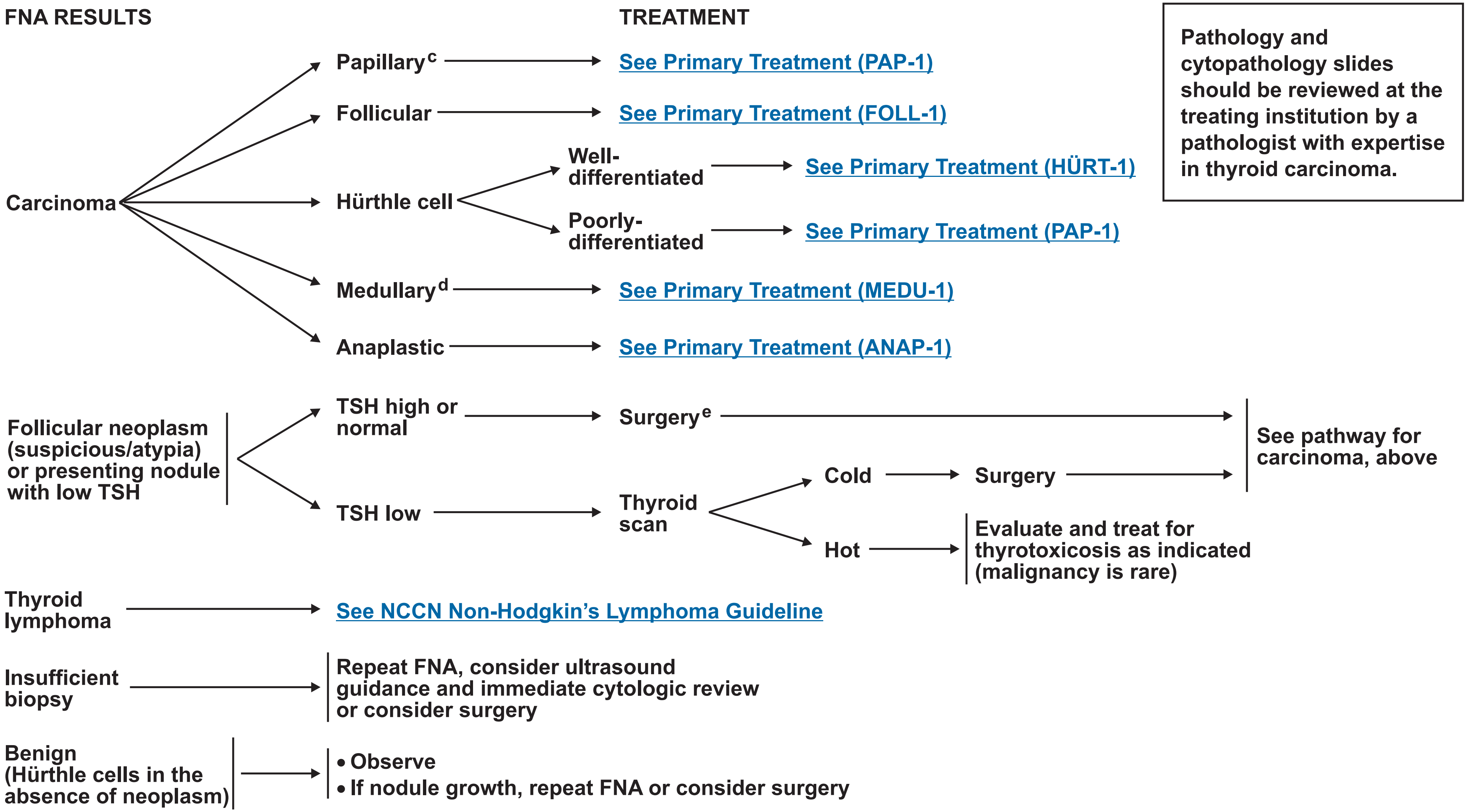
Nodule Evaluation



FNA RESULTS → **TREATMENT**

- Carcinoma
  - Papillary[c] → See Primary Treatment (PAP-1)
  - Follicular → See Primary Treatment (FOLL-1)
  - Hürthle cell
    - Well-differentiated → See Primary Treatment (HÜRT-1)
    - Poorly-differentiated → See Primary Treatment (PAP-1)
  - Medullary[d] → See Primary Treatment (MEDU-1)
  - Anaplastic → See Primary Treatment (ANAP-1)
- Follicular neoplasm (suspicious/atypia) or presenting nodule with low TSH
  - TSH high or normal → Surgery[e] → See pathway for carcinoma, above
  - TSH low → Thyroid scan
    - Cold → Surgery → See pathway for carcinoma, above
    - Hot → Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)
- Thyroid lymphoma → See NCCN Non-Hodgkin's Lymphoma Guideline
- Insufficient biopsy → Repeat FNA, consider ultrasound guidance and immediate cytologic review or consider surgery
- Benign (Hürthle cells in the absence of neoplasm) →
  - Observe
  - If nodule growth, repeat FNA or consider surgery

Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in thyroid carcinoma.

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[c] This includes cytology suspicious for papillary carcinoma.

[d] If suspicious, perform serum calcitonin and CEA.

[e] Consider trial of thyroxine therapy for small, clinically nonsuspicious, follicular neoplasm in a young female patient (category 3).

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Papillary Carcinoma

FNA FINDING

Papillary carcinoma FNA positive →

DIAGNOSTIC PROCEDURES

- Consider chest x-ray
- Thyroid ultrasound, if not previously done
- Consider lateral neck ultrasound (category 2B)
- CT/MRI for fixed or substernal lesions (avoid iodinated contrast, unless essential)
- Evaluate vocal cord mobility (category 2B)

PREOPERATIVE OR INTRAOPERATIVE DECISION-MAKING CRITERIA / **PRIMARY TREATMENT**

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

→ Total thyroidectomy
If lymph node(s) palpable or biopsy positive:
- Central neck dissection (level VI)
- Lateral neck dissection (levels II-V, sparing spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle)
  Consider preservation of the cervical sensory nerves, when feasible

→ See Postsurgical Evaluation (PAP-3)

Indications for total thyroidectomy or lobectomy:
(all present)
- Age 15 y - 45 y[a]
- No prior radiation
- No distant metastases
- No cervical lymph node metastases
- No extrathyroidal extension
- Tumor < 4 cm in diameter
- No aggressive variant[b]

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

or

Lobectomy + isthmusectomy (category 2B)
- Aggressive variant[b]
- Macroscopic multifocal disease
- Positive isthmus margins
- Cervical lymph node metastases
- Extrathyroidal extension

  → Completion of thyroidectomy → See Postsurgical Evaluation (PAP-3)
- Negative margins
- No contralateral lesion

  →
  - Consider thyroglobulin measurement
  - Suppress TSH with thyroxine

  → See Surveillance and Maintenance (PAP-5)

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[a] Age is an approximation and not an absolute determination.

[b] Tall cell, columnar cell, insular, oxyphilic, or poorly differentiated features.

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Papillary Carcinoma

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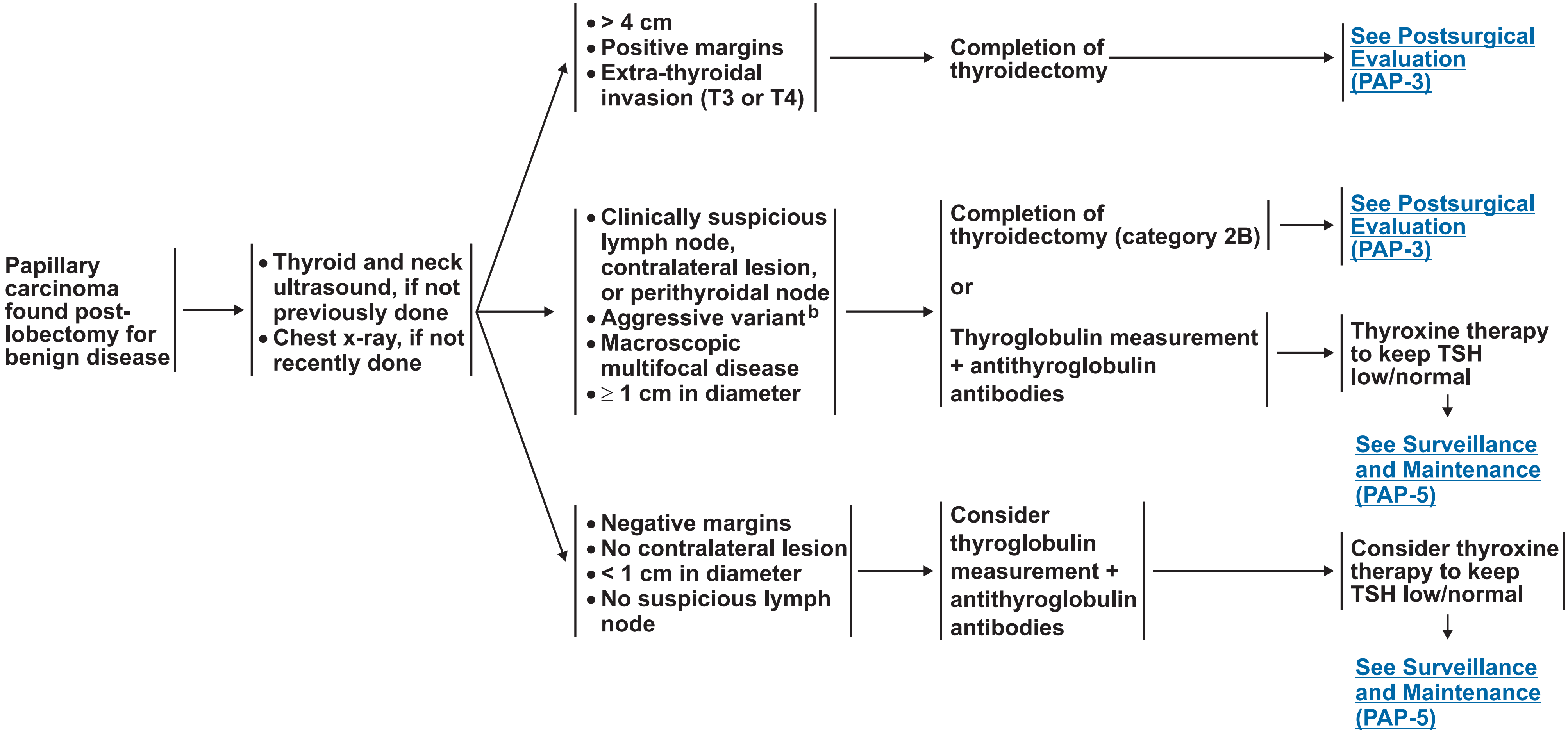
CLINICAL PRESENTATION

PRIMARY TREATMENT



Papillary carcinoma found post-lobectomy for benign disease →

- Thyroid and neck ultrasound, if not previously done
- Chest x-ray, if not recently done

→

- > 4 cm
- Positive margins
- Extra-thyroidal invasion (T3 or T4)

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

- Clinically suspicious lymph node, contralateral lesion, or perithyroidal node
- Aggressive variant[b]
- Macroscopic multifocal disease
- ≥ 1 cm in diameter

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

or

Thyroglobulin measurement + antithyroglobulin antibodies → Thyroxine therapy to keep TSH low/normal → See Surveillance and Maintenance (PAP-5)

- Negative margins
- No contralateral lesion
- < 1 cm in diameter
- No suspicious lymph node

→ Consider thyroglobulin measurement + antithyroglobulin antibodies → Consider thyroxine therapy to keep TSH low/normal → See Surveillance and Maintenance (PAP-5)

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[b] Tall cell, columnar cell, insular, oxyphilic, or poorly differentiated features.

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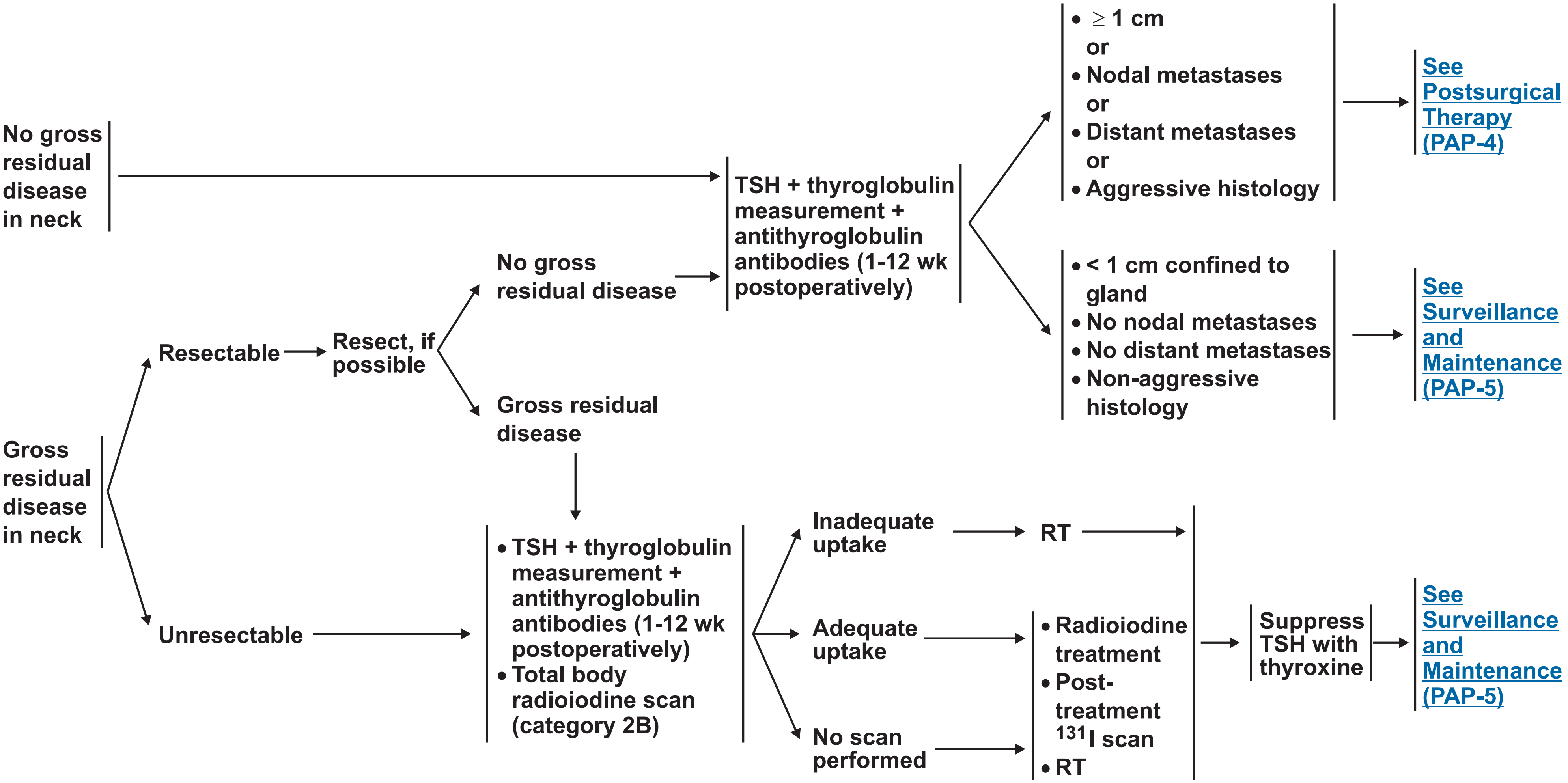
POSTSURGICAL EVALUATION AFTER THYROIDECTOMY



No gross residual disease in neck → TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)

- ≥ 1 cm or
- Nodal metastases or
- Distant metastases or
- Aggressive histology

→ See Postsurgical Therapy (PAP-4)

- < 1 cm confined to gland
- No nodal metastases
- No distant metastases
- Non-aggressive histology

→ See Surveillance and Maintenance (PAP-5)

Gross residual disease in neck

Resectable → Resect, if possible

- No gross residual disease → TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)
- Gross residual disease ↓

Unresectable →

- TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)
- Total body radioiodine scan (category 2B)

Inadequate uptake → RT →

Adequate uptake →

No scan performed →

- Radioiodine treatment
- Post-treatment ^{131}I scan
- RT

→ Suppress TSH with thyroxine → See Surveillance and Maintenance (PAP-5)

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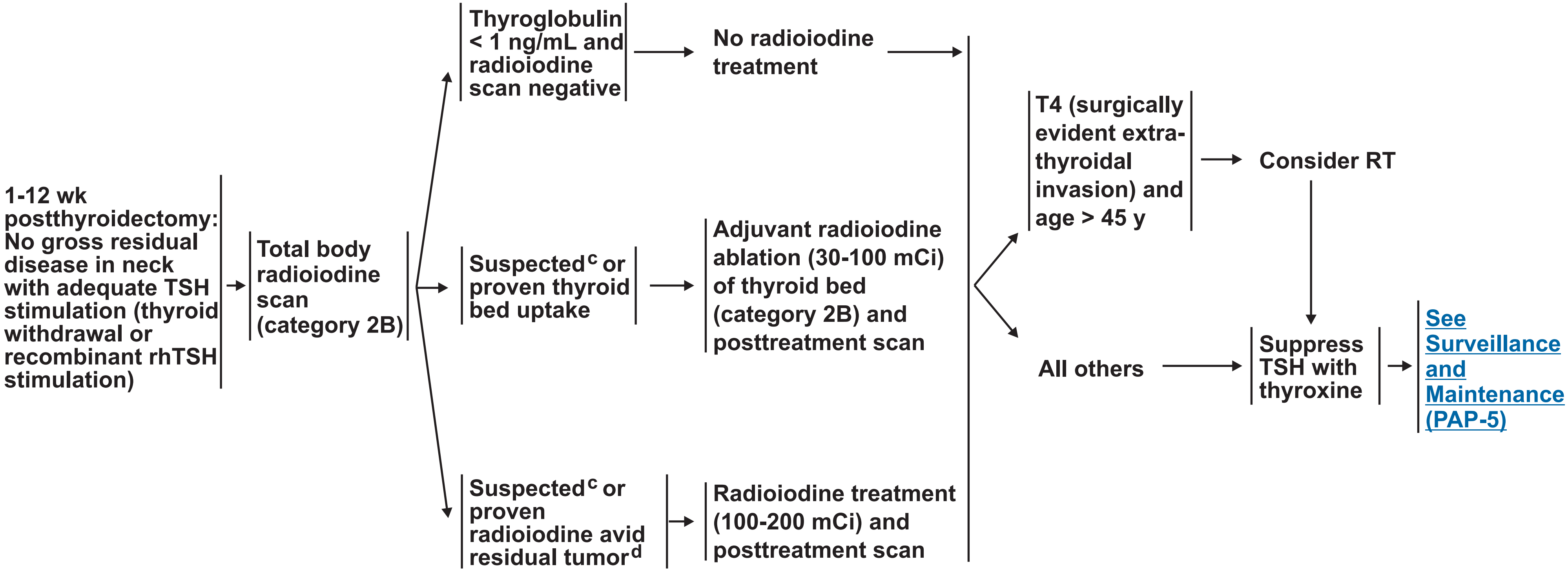
POSTSURGICAL THERAPY



1-12 wk postthyroidectomy: No gross residual disease in neck with adequate TSH stimulation (thyroid withdrawal or recombinant rhTSH stimulation) → **Total body radioiodine scan (category 2B)**

- **Thyroglobulin < 1 ng/mL and radioiodine scan negative** → **No radioiodine treatment**
- **Suspected[c] or proven thyroid bed uptake** → **Adjuvant radioiodine ablation (30-100 mCi) of thyroid bed (category 2B) and posttreatment scan**
- **Suspected[c] or proven radioiodine avid residual tumor[d]** → **Radioiodine treatment (100-200 mCi) and posttreatment scan**

→
- **T4 (surgically evident extra-thyroidal invasion) and age > 45 y** → **Consider RT** → **Suppress TSH with thyroxine**
- **All others** → **Suppress TSH with thyroxine** → **See Surveillance and Maintenance (PAP-5)**

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

[d] All patients should be examined and palpable neck disease should be surgically resected before radioiodine treatment.

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and thyroglobulin measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound
- TSH stimulated thyroglobulin without radioiodine scan at 12 mo in patients previously treated with RAI with recent negative neck ultrasound and undetectable TSH suppressed thyroglobulin (anti-thyroglobulin antibody negative) and T1-2, N0-1, M0 at initial staging
- If detectable thyroglobulin, distant metastases or soft tissue invasion on initial staging, radioiodine scan every 12 mo until no radioactive iodine avid tumor is evident (either withdrawal of thyroid hormone or rhTSH)[e]
- Consider additional nonradioiodine imaging (eg, FDG PET ± CT if Tg $\geq$ 10 ng/mL), if ^{131}I scans negative and stimulated Tg > 2-5 ng/mL

RECURRENT DISEASE

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

→ Suppress TSH with thyroxine

Locoregional recurrence → Surgery (preferred) if resectable
and/or
Radioiodine treatment, if radioiodine scan positive
and/or
RT

- Thyroglobulin > 10 ng/mL (off thyroid hormone)
- Scans (including PET) negative

→ Consider radioiodine therapy with 100-150 mCi, posttreatment ^{131}I scan (category 3)

Metastatic disease → See Treatment of Metastases (PAP-6)

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

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TREATMENT OF METASTASES

Metastatic disease
- **Continue to suppress TSH with thyroxine**

Solitary CNS →

Consider neurosurgical resection
and/or
Radioiodine treatment with rhTSH and steroid prophylaxis, if radioiodine scan positive
and/or
RT

Bone →

- **Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities**
  and/or
  Radioiodine treatment, if radioiodine scan positive
  and/or
  RT
- **Consider bisphosphonate therapy**
- **Consider embolization of metastases**

Other extracervical sites →

Consider surgical resection of selected, enlarging, or symptomatic metastases
and/or
Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing
and/or
Clinical trials for non-radioiodine avid tumors[f]; systemic therapy if not in clinical trial
or
Best Supportive Care

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[f] Cytotoxic chemotherapy has shown to have minimal efficacy. There are agents in clinical trials investigating novel targeted therapies. See Clinical trials available at the NCCN member institutions.

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Follicular Carcinoma

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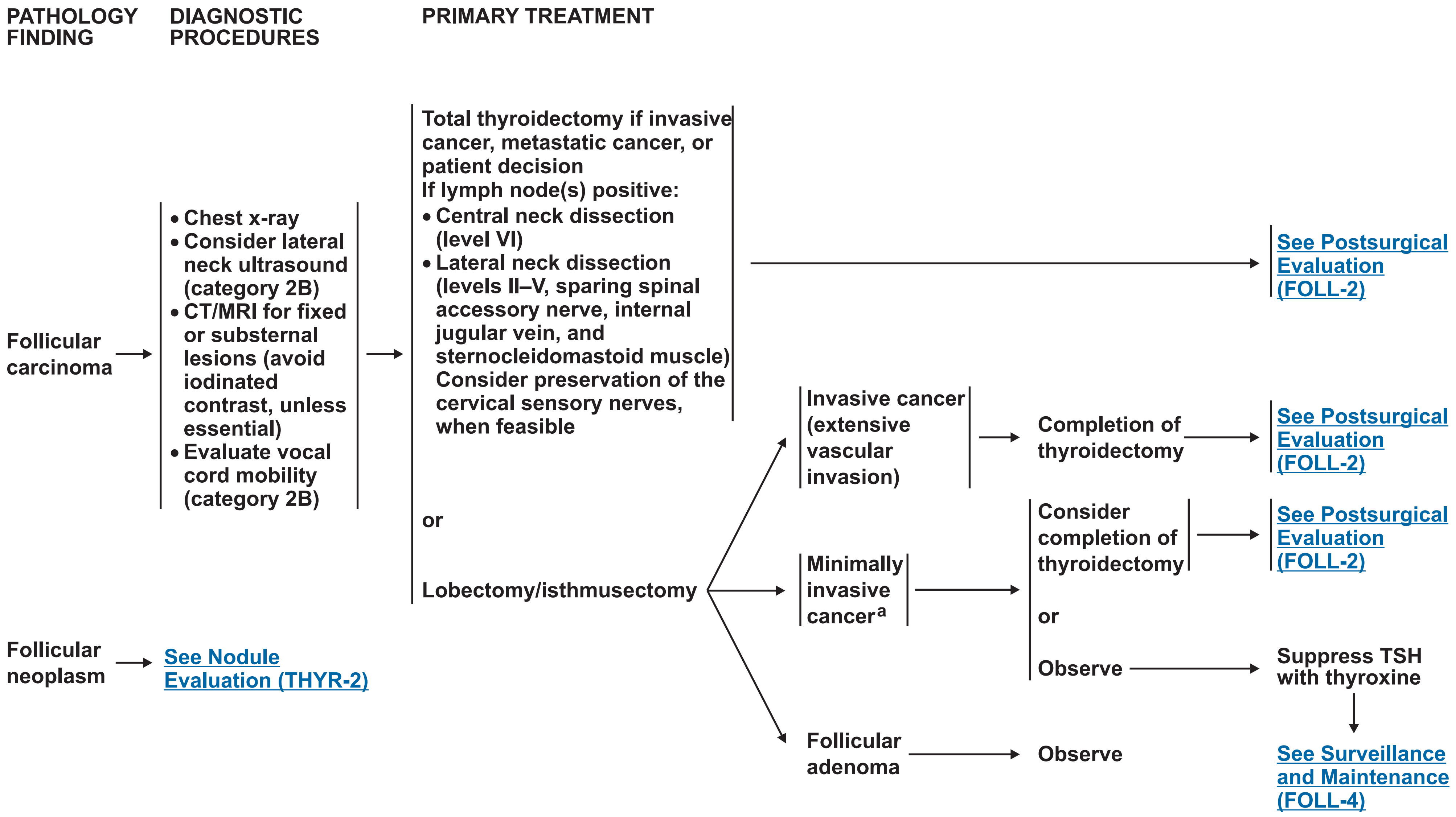

PATHOLOGY FINDING | **DIAGNOSTIC PROCEDURES** | **PRIMARY TREATMENT**

Follicular carcinoma →

- Chest x-ray
- Consider lateral neck ultrasound (category 2B)
- CT/MRI for fixed or substernal lesions (avoid iodinated contrast, unless essential)
- Evaluate vocal cord mobility (category 2B)

→

Total thyroidectomy if invasive cancer, metastatic cancer, or patient decision
If lymph node(s) positive:
- Central neck dissection (level VI)
- Lateral neck dissection (levels II–V, sparing spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle)
Consider preservation of the cervical sensory nerves, when feasible

→ See Postsurgical Evaluation (FOLL-2)

or

Lobectomy/isthmusectomy →
- Invasive cancer (extensive vascular invasion) → Completion of thyroidectomy → See Postsurgical Evaluation (FOLL-2)
- Minimally invasive cancer[a] →
  - Consider completion of thyroidectomy → See Postsurgical Evaluation (FOLL-2)
  - or
  - Observe → Suppress TSH with thyroxine → See Surveillance and Maintenance (FOLL-4)
- Follicular adenoma → Observe

Follicular neoplasm → See Nodule Evaluation (THYR-2)

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[a] 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.

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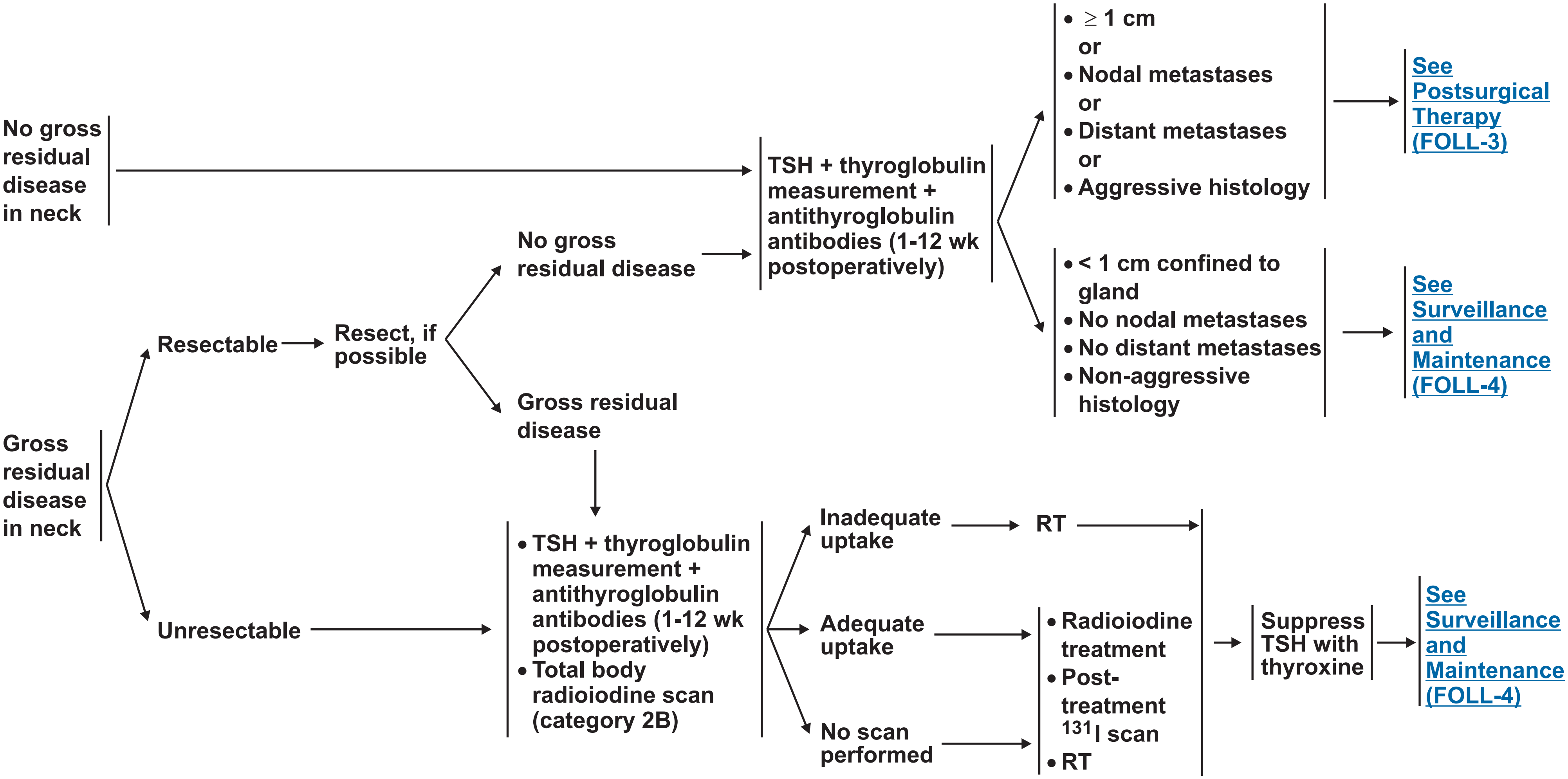
POSTSURGICAL EVALUATION AFTER THYROIDECTOMY



No gross residual disease in neck → **TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)**

Gross residual disease in neck
- **Resectable** → **Resect, if possible**
  - **No gross residual disease** → **TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)**
  - **Gross residual disease** → see below
- **Unresectable** → see below

TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)
- **• ≥ 1 cm or • Nodal metastases or • Distant metastases or • Aggressive histology** → **See Postsurgical Therapy (FOLL-3)**
- **• < 1 cm confined to gland • No nodal metastases • No distant metastases • Non-aggressive histology** → **See Surveillance and Maintenance (FOLL-4)**

Gross residual disease / Unresectable → **• TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively) • Total body radioiodine scan (category 2B)**
- **Inadequate uptake** → **RT** → **Suppress TSH with thyroxine** → **See Surveillance and Maintenance (FOLL-4)**
- **Adequate uptake** → **• Radioiodine treatment • Post-treatment ^{131}I scan • RT** → **Suppress TSH with thyroxine** → **See Surveillance and Maintenance (FOLL-4)**
- **No scan performed** → **• Radioiodine treatment • Post-treatment ^{131}I scan • RT** → **Suppress TSH with thyroxine** → **See Surveillance and Maintenance (FOLL-4)**

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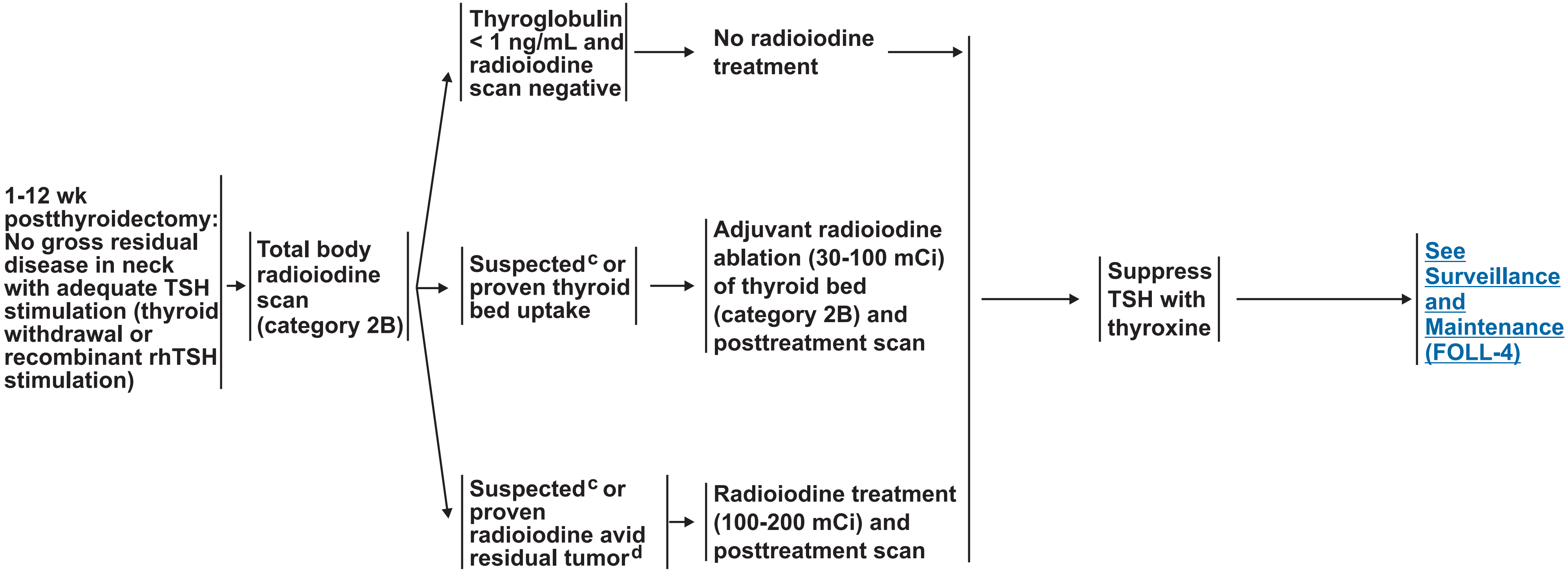

1-12 wk postthyroidectomy: No gross residual disease in neck with adequate TSH stimulation (thyroid withdrawal or recombinant rhTSH stimulation) → Total body radioiodine scan (category 2B)

- Thyroglobulin < 1 ng/mL and radioiodine scan negative → No radioiodine treatment →
- Suspected[c] or proven thyroid bed uptake → Adjuvant radioiodine ablation (30-100 mCi) of thyroid bed (category 2B) and posttreatment scan →
- Suspected[c] or proven radioiodine avid residual tumor[d] → Radioiodine treatment (100-200 mCi) and posttreatment scan →

→ Suppress TSH with thyroxine → See Surveillance and Maintenance (FOLL-4)

---

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

[d] All patients should be examined and palpable neck disease should be surgically resected before radioiodine treatment.

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and thyroglobulin measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- TSH stimulated thyroglobulin without radioiodine scan at 12 mo in patients previously treated with RAI with recent negative neck ultrasound and undetectable TSH suppressed thyroglobulin (anti-thyroglobulin antibody negative) and T1-2, N0-1, M0 at initial staging
- If detectable thyroglobulin, distant metastases or soft tissue invasion on initial staging, radioiodine scan every 12 mo until no radioactive iodine avid tumor is evident (either withdrawal of thyroid hormone or rhTSH)[e]
- Consider additional nonradioiodine imaging (eg, FDG PET ± CT if Tg ≥ 10 ng/mL), if ^{131}I scans negative and stimulated Tg > 2-5 ng/mL

RECURRENT DISEASE

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

→ Suppress TSH with thyroxine

Locoregional recurrence → Surgery (preferred) if resectable
and/or
radioiodine treatment,
if radioiodine scan positive
and/or
RT

- Thyroglobulin > 10 ng/mL (off thyroid hormone)
- Scans (including PET) negative

→ Consider radioiodine therapy with 100-150 mCi, posttreatment ^{131}I scan (category 3)

Metastatic disease → See Treatment of Metastases (FOLL-5)

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

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TREATMENT OF METASTASES

Metastatic disease
- Continue to suppress TSH with thyroxine

Solitary CNS →

Consider neurosurgical resection
and/or
Radioiodine treatment with rhTSH and steroid prophylaxis, if radioiodine scan positive
and/or
RT

Bone →

- Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities
  and/or
  Radioiodine treatment, if radioiodine scan positive
  and/or
  RT
- Consider bisphosphonate therapy
- Consider embolization of metastases

Other extracervical sites →

Consider surgical resection of selected, enlarging, or symptomatic metastases
and/or
Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing
and/or
Clinical trials for non-radioiodine avid tumors;[f] systemic therapy if not in clinical trial
or
Best Supportive Care

---

[f] Cytotoxic chemotherapy has shown to have minimal efficacy. There are agents in clinical trials investigating novel targeted therapies. See Clinical trials available at the NCCN member institutions.

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Hürthle Cell Carcinoma

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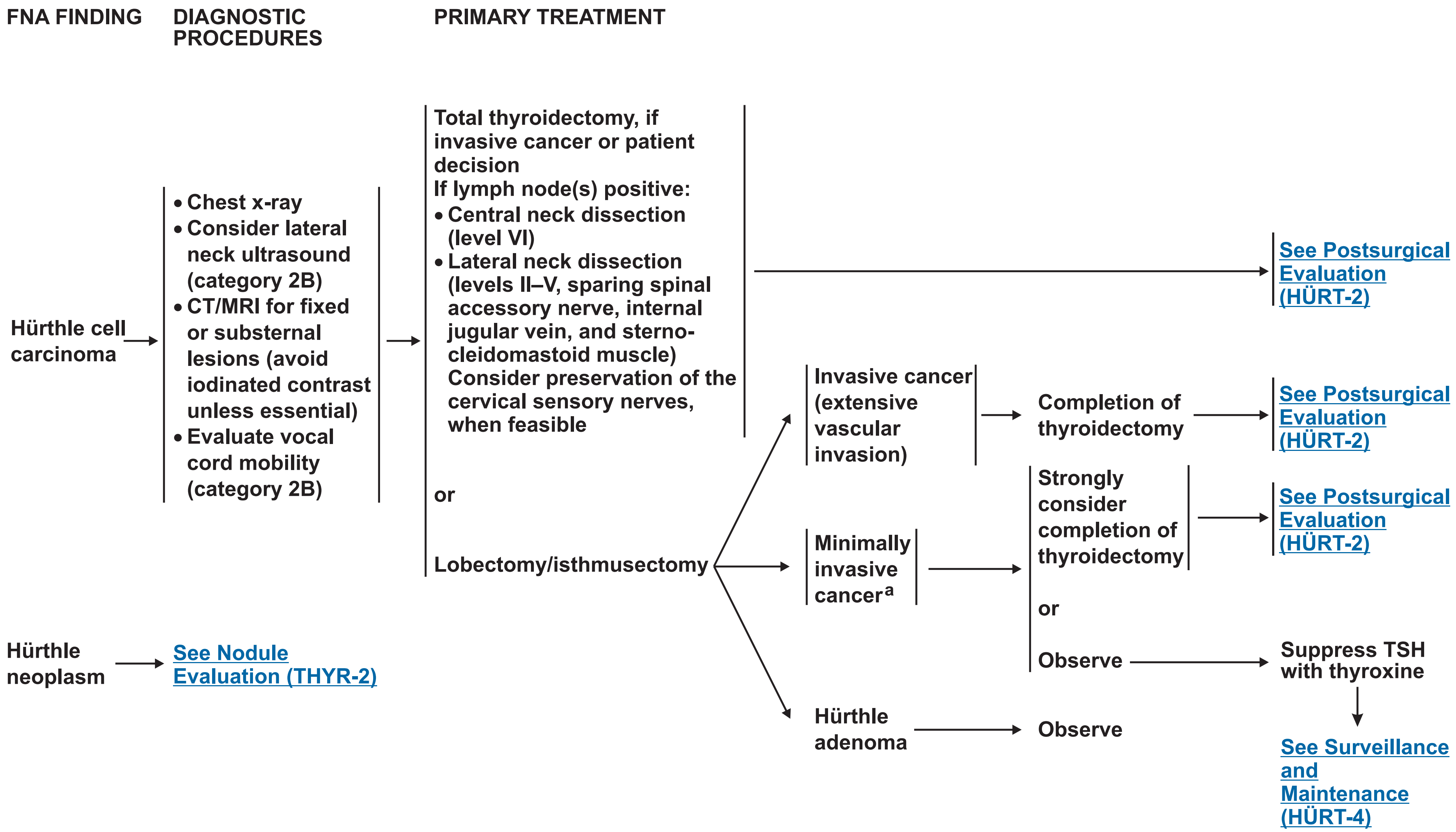
Thyroid Carcinoma TOC
Staging, MS, References



FNA FINDING → **DIAGNOSTIC PROCEDURES** → **PRIMARY TREATMENT**

Hürthle cell carcinoma →
- Chest x-ray
- Consider lateral neck ultrasound (category 2B)
- CT/MRI for fixed or substernal lesions (avoid iodinated contrast unless essential)
- Evaluate vocal cord mobility (category 2B)

→ Total thyroidectomy, if invasive cancer or patient decision
If lymph node(s) positive:
- Central neck dissection (level VI)
- Lateral neck dissection (levels II–V, sparing spinal accessory nerve, internal jugular vein, and sterno-cleidomastoid muscle) Consider preservation of the cervical sensory nerves, when feasible

→ See Postsurgical Evaluation (HÜRT-2)

or

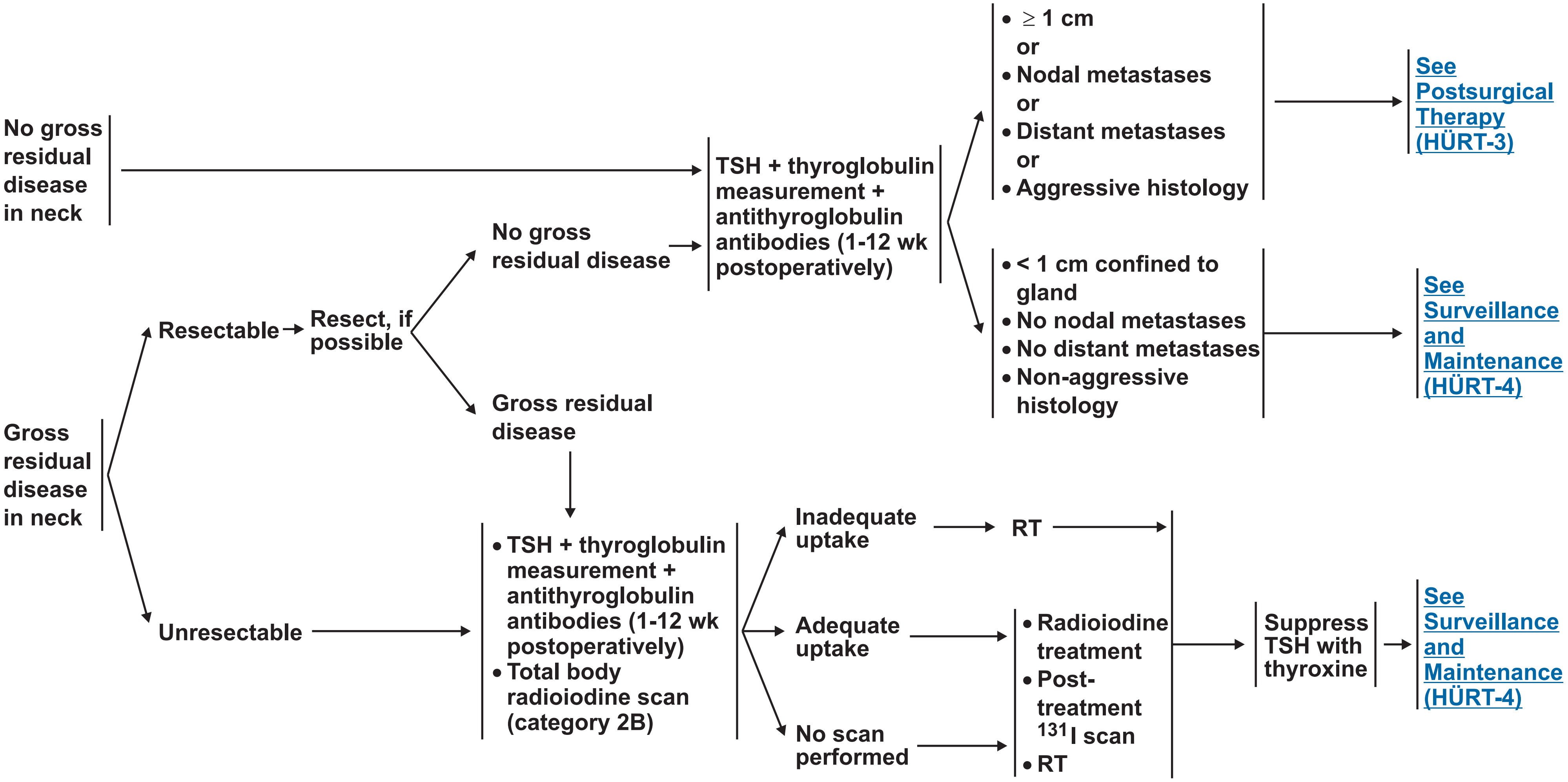
Lobectomy/isthmusectomy
- → Invasive cancer (extensive vascular invasion) → Completion of thyroidectomy → See Postsurgical Evaluation (HÜRT-2)
- → Minimally invasive cancer[a] →
  - Strongly consider completion of thyroidectomy → See Postsurgical Evaluation (HÜRT-2)
  - or
  - Observe → Suppress TSH with thyroxine → See Surveillance and Maintenance (HÜRT-4)
- → Hürthle adenoma → Observe

Hürthle neoplasm → See Nodule Evaluation (THYR-2)

[a] 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.

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

POSTSURGICAL EVALUATION AFTER THYROIDECTOMY



- No gross residual disease in neck → TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)
  - • ≥ 1 cm or • Nodal metastases or • Distant metastases or • Aggressive histology → See Postsurgical Therapy (HÜRT-3)
  - • < 1 cm confined to gland • No nodal metastases • No distant metastases • Non-aggressive histology → See Surveillance and Maintenance (HÜRT-4)
- Gross residual disease in neck
  - Resectable → Resect, if possible
    - No gross residual disease → TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively)
    - Gross residual disease → see Unresectable pathway below
  - Unresectable → • TSH + thyroglobulin measurement + antithyroglobulin antibodies (1-12 wk postoperatively) • Total body radioiodine scan (category 2B)
    - Inadequate uptake → RT → Suppress TSH with thyroxine → See Surveillance and Maintenance (HÜRT-4)
    - Adequate uptake → • Radioiodine treatment • Post-treatment ^{131}I scan • RT → Suppress TSH with thyroxine → See Surveillance and Maintenance (HÜRT-4)
    - No scan performed → • Radioiodine treatment • Post-treatment ^{131}I scan • RT → Suppress TSH with thyroxine → See Surveillance and Maintenance (HÜRT-4)

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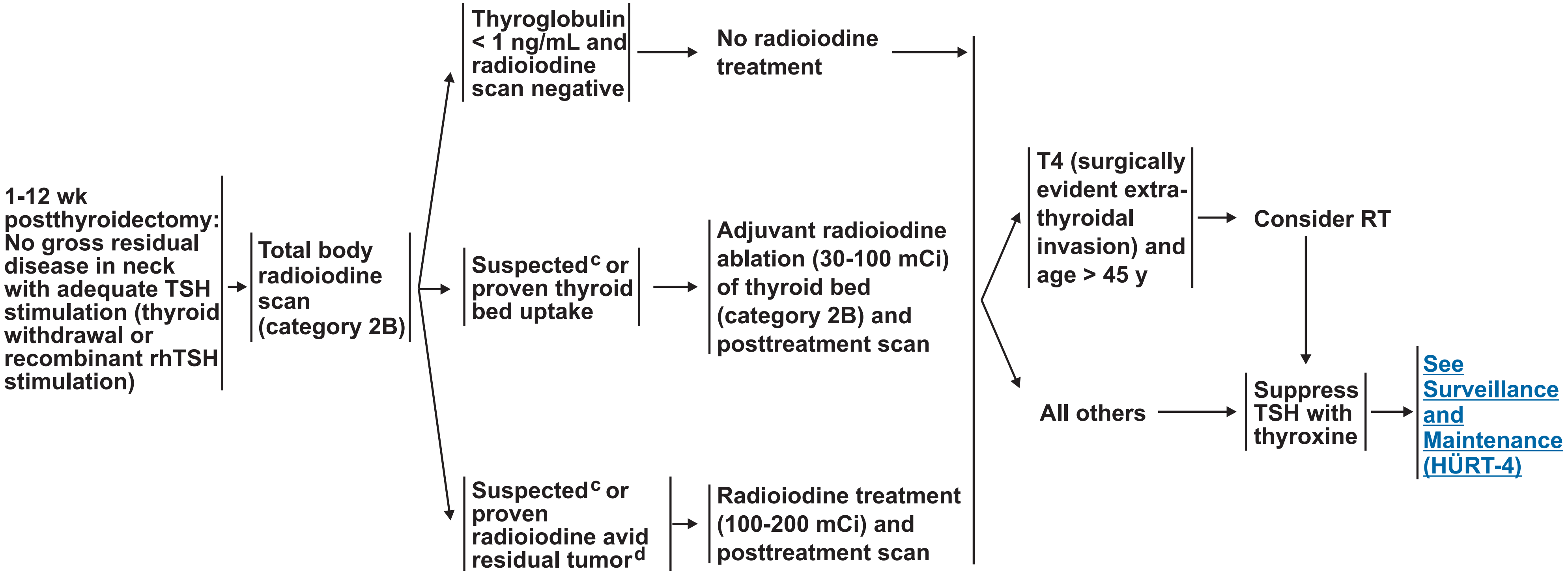
POSTSURGICAL THERAPY



1-12 wk postthyroidectomy: No gross residual disease in neck with adequate TSH stimulation (thyroid withdrawal or recombinant rhTSH stimulation) → **Total body radioiodine scan (category 2B)**

- **Thyroglobulin < 1 ng/mL and radioiodine scan negative** → **No radioiodine treatment**
- **Suspected[c] or proven thyroid bed uptake** → **Adjuvant radioiodine ablation (30-100 mCi) of thyroid bed (category 2B) and posttreatment scan**
- **Suspected[c] or proven radioiodine avid residual tumor[d]** → **Radioiodine treatment (100-200 mCi) and posttreatment scan**

All of the above →

- **T4 (surgically evident extra-thyroidal invasion) and age > 45 y** → **Consider RT** → **Suppress TSH with thyroxine**
- **All others** → **Suppress TSH with thyroxine**

→ **See Surveillance and Maintenance (HÜRT-4)**

[c] Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.
[d] All patients should be examined and palpable neck disease should be surgically resected before radioiodine treatment.

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SURVEILLANCE AND MAINTENANCE

- Physical examination, TSH and thyroglobulin measurement + antithyroglobulin antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound
- TSH stimulated thyroglobulin without radioiodine scan at 12 mo in patients previously treated with RAI with recent negative neck ultrasound and undetectable TSH suppressed thyroglobulin (anti-thyroglobulin antibody negative) and T1-2, N0-1, M0 at initial staging
- If detectable thyroglobulin, distant metastases or soft tissue invasion on initial staging, radioiodine scan every 12 mo until no radioactive iodine avid tumor is evident (either withdrawal of thyroid hormone or rhTSH)[e]
- Consider additional nonradioiodine imaging (eg, FDG PET ± CT if Tg ≥ 10 ng/mL), if ^{131}I scans negative and stimulated Tg > 2-5 ng/mL

RECURRENT DISEASE

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

→ Suppress TSH with thyroxine

Locoregional recurrence → Surgery (preferred) if resectable
and/or
Radioiodine treatment, if radioiodine scan positive
and/or
RT, if radioiodine scan negative

- Thyroglobulin > 10 ng/mL (off thyroid hormone)
- Scans (including PET) negative

→ Consider radioiodine therapy with 100-150 mCi, posttreatment ^{131}I scan (category 2B)

Metastatic disease → See Treatment of Metastases (HÜRT-5)

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

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TREATMENT OF METASTASES

Metastatic disease
- **Continue to suppress TSH with thyroxine**

Solitary CNS → **Consider neurosurgical resection**
and/or
RT

Bone →
- **Surgical resection, if symptomatic or asymptomatic in weight-bearing extremities**
  and/or
  RT
- **Consider bisphosphonate therapy**
- **Consider embolization of metastases**

Other extracervical sites → **Consider surgical resection of selected, enlarging, or symptomatic metastases**
and/or
Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing
and/or
Clinical trials for non-radioiodine avid tumors;[f] systemic therapy if not in clinical trial
or
Best Supportive Care

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[f] Cytotoxic chemotherapy has shown to have minimal efficacy. There are agents in clinical trials investigating novel targeted therapies.
See Clinical trials available at the NCCN member institutions.

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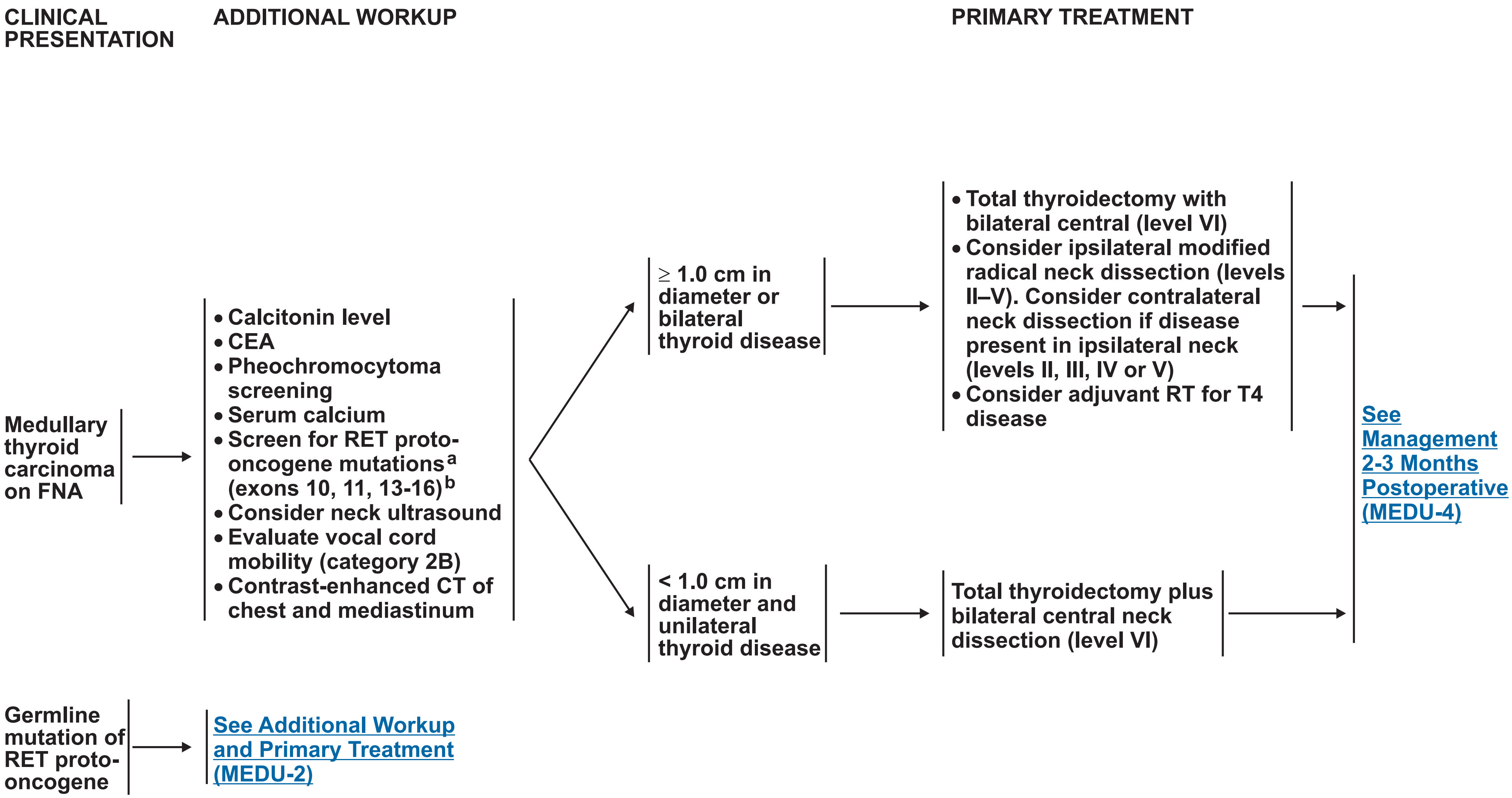
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Medullary Carcinoma



CLINICAL PRESENTATION

ADDITIONAL WORKUP

PRIMARY TREATMENT

Medullary thyroid carcinoma on FNA →

- Calcitonin level
- CEA
- Pheochromocytoma screening
- Serum calcium
- Screen for RET proto-oncogene mutations[a] (exons 10, 11, 13-16)[b]
- Consider neck ultrasound
- Evaluate vocal cord mobility (category 2B)
- Contrast-enhanced CT of chest and mediastinum

→ ≥ 1.0 cm in diameter or bilateral thyroid disease →

- Total thyroidectomy with bilateral central (level VI)
- Consider ipsilateral modified radical neck dissection (levels II–V). Consider contralateral neck dissection if disease present in ipsilateral neck (levels II, III, IV or V)
- Consider adjuvant RT for T4 disease

→ < 1.0 cm in diameter and unilateral thyroid disease → Total thyroidectomy plus bilateral central neck dissection (level VI)

→ See Management 2-3 Months Postoperative (MEDU-4)

Germline mutation of RET proto-oncogene → See Additional Workup and Primary Treatment (MEDU-2)

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[a] Germline mutation should prompt family testing of first-degree relatives and counseling.

[b] If exons 10, 11, 13-16 negative, evaluate for exon 8.

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Medullary Carcinoma

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

Germline mutation of RET proto-oncogene

→ **MEN 2B (codon 883, 918, or 922 RET mutations)**

→
- **Calcitonin level**
- **CEA**
- **Pheochromocytoma screening**[d,e]

→
- **Total thyroidectomy during the first year of life or at diagnosis + bilateral central neck dissection (level VI)**
- **Consider more extensive node dissection (levels II–V) if tumor(s) > 0.5 cm in diameter**
- **Consider adjuvant RT for T4 disease**

→ **See Management 2-3 Months Postoperative (MEDU-4)**

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

→
- **Basal calcitonin level**
- **Calcium stimulated calcitonin test if calcitonin undetectable (category 2B for use in timing of surgery)**
- **CEA**
- **Pheochromocytoma screening**[d,e]
- **Serum calcium**
- **Consider neck ultrasound (category 2B)**

→ **See Primary Treatment (MEDU-3)**

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[c] Lethality of medullary thyroid carcinoma associated with codon 768, 790, 791, and 804 RET mutations may be lower than with other RET mutations. In patients with these RET mutations, annual provocative (calcium) calcitonin testing may be performed, with total thyroidectomy and central node dissection deferred until tests become abnormal after the age of 5. 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 2002;87(6)5658-71.

[d] Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.

[e] Screening for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A) should be performed annually. For some RET mutations (codons 768, 790, V804M, or 891) less frequent screening may be appropriate.

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Medullary Carcinoma

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CLINICAL PRESENTATION

PRIMARY TREATMENT

MEN 2A or Familial medullary thyroid carcinoma → **Measure serum intact parathyroid hormone**

Suppressed → **Evaluate for other causes of hypercalcemia** →

- **Total thyroidectomy by age 5 or when mutation identified**[c]
- **Consider bilateral central neck dissection (level VI) if elevated calcitonin or CEA test or ultrasound identified thyroid or nodal abnormality**
- **Consider more extensive lymph node dissection (levels II–V) if tumor(s) > 1.0 cm or central node(s) positive**
- **Consider adjuvant RT for T4 disease in adults**

→ **See Management 2-3 Months Postoperative (MEDU-4)**

Not suppressed →

- **Total thyroidectomy by age 5 or when mutation identified**[c]
- **Consider bilateral central neck dissection (level VI) if elevated calcitonin or CEA test or ultrasound identified thyroid or nodal abnormality**
- **Consider more extensive lymph node dissection (levels II–V) if tumor(s) > 1.0 cm or central node(s) positive**
- **During primary operative procedure and parathyroid exploration:**
  - **If single adenoma, excise**
  - **If multiglandular hyperplasia, leave, or autotransplant the equivalent mass of one normal parathyroid**
  - **Consider cryopreservation of parathyroid tissue**
- **Consider adjuvant RT for T4 disease in adults**

→ **See Management 2-3 Months Postoperative (MEDU-4)**

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[c] Lethality of medullary thyroid carcinoma associated with codon 768, 790, 791, and 804 RET mutations may be lower than with other RET mutations. In patients with these RET mutations, annual provocative (calcium) calcitonin testing may be performed, with total thyroidectomy and central node dissection deferred until tests become abnormal after the age of 5. 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 2002;87(6)5658-71.

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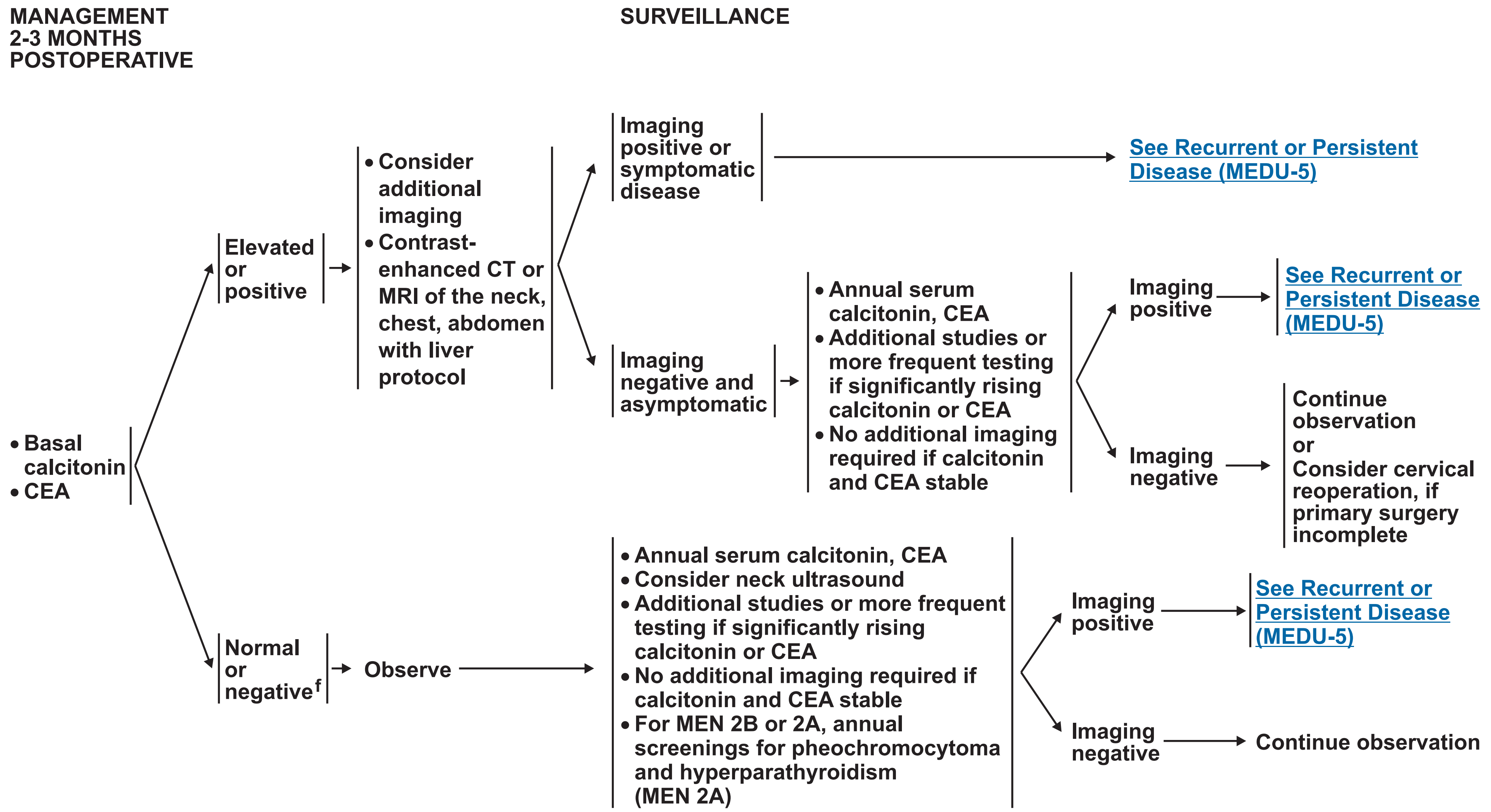
Medullary Carcinoma



MANAGEMENT 2-3 MONTHS POSTOPERATIVE

SURVEILLANCE

- Basal calcitonin
- CEA

Elevated or positive →
- Consider additional imaging
- Contrast-enhanced CT or MRI of the neck, chest, abdomen with liver protocol

→ **Imaging positive or symptomatic disease** → See Recurrent or Persistent Disease (MEDU-5)

→ **Imaging negative and asymptomatic** →
- Annual serum calcitonin, CEA
- Additional studies or more frequent testing if significantly rising calcitonin or CEA
- No additional imaging required if calcitonin and CEA stable

→ Imaging positive → See Recurrent or Persistent Disease (MEDU-5)

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

Normal or negative[f] → Observe →
- Annual serum calcitonin, CEA
- Consider neck 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-5)

→ Imaging negative → Continue observation

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[f] The likelihood of significant residual disease with a negative basal calcitonin is very low.

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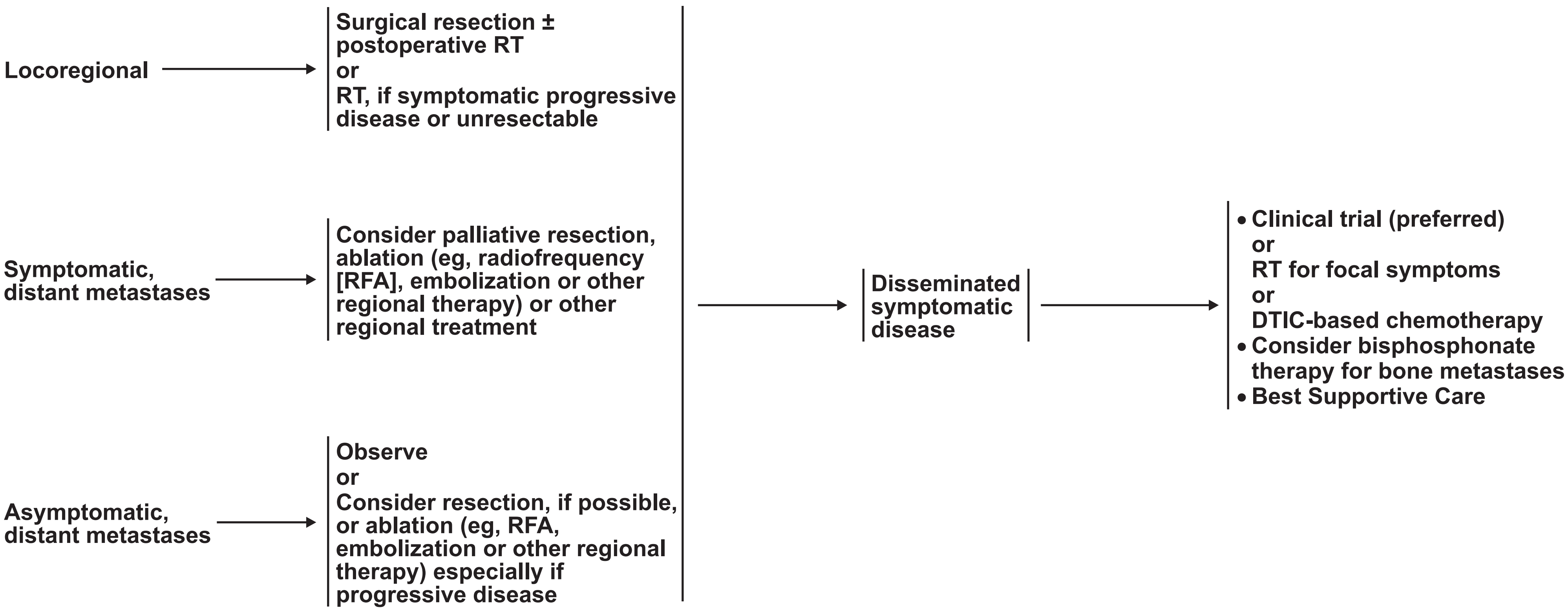
RECURRENT OR PERSISTENT DISEASE



Locoregional → Surgical resection ± postoperative RT
or
RT, if symptomatic progressive disease or unresectable

Symptomatic, distant metastases → Consider palliative resection, ablation (eg, radiofrequency [RFA], embolization or other regional therapy) or other regional treatment

Asymptomatic, distant metastases → Observe
or
Consider resection, if possible, or ablation (eg, RFA, embolization or other regional therapy) especially if progressive disease

→ Disseminated symptomatic disease →
- Clinical trial (preferred)
  or
  RT for focal symptoms
  or
  DTIC-based chemotherapy
- Consider bisphosphonate therapy for bone metastases
- Best Supportive Care

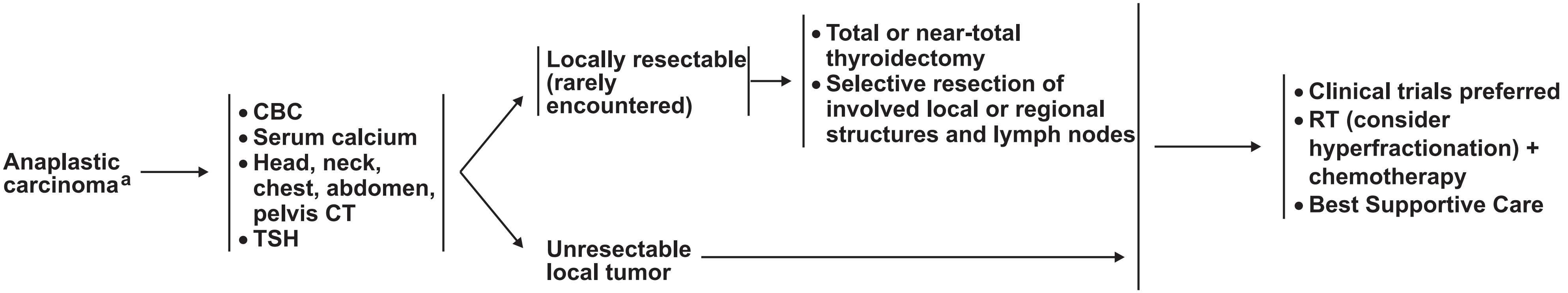
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Anaplastic Carcinoma

FNA OR CORE BIOPSY FINDING

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT



Anaplastic carcinoma[a] →

- CBC
- Serum calcium
- Head, neck, chest, abdomen, pelvis CT
- TSH

→ **Locally resectable (rarely encountered)** →

- Total or near-total thyroidectomy
- Selective resection of involved local or regional structures and lymph nodes

→ **Unresectable local tumor** →

→

- Clinical trials preferred
- RT (consider hyperfractionation) + chemotherapy
- Best Supportive Care

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[a] An FNA diagnosis of anaplastic carcinoma should be confirmed by core biopsy.

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.

Staging (2002 AJCC 6th Edition)

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging For Thyroid Cancer

Primary Tumor (T)

Note: All categories may be subdivided: (A) solitary tumor, (b) 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
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	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

All anaplastic carcinomas are considered T4 tumors.

T4a	Intrathyroidal anaplastic carcinoma –surgically resectable
T4b	Extrathyroidal anaplastic carcinoma – surgically unresectable

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 or superior mediastinal lymph nodes

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping:

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

Papillary or Follicular

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

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

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

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Histopathologic Type

There are four major histopathologic types:

- Papillary carcinoma (including follicular variant of papillary carcinoma)
- Follicular carcinoma (including Hurthle cell carcinoma)
- Medullary carcinoma
- Undifferentiated (anaplastic) carcinoma

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Epidemiology

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

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is about 1% (0.84% for women and 0.30% for men).[5] Approximately 30,180 new cases of thyroid carcinoma will be diagnosed in the United States in the year 2006, and the prevalence estimate is about 292,555.[6,7] As with thyroid nodules, this cancer occurs two to three times more often in women than in men. With the incidence increasing by 4% per year, thyroid cancer is currently the eighth most common malignancy diagnosed in women. Among persons aged 15 to 24 years, thyroid cancer accounts for 7.5% to 10% of all diagnosed malignancies.[8] The disease is also diagnosed more often in white North Americans than in African Americans. Although thyroid carcinoma can occur at any age, the peak incidence is around age 50 to 54 years in women and 65 to 69 years in men for the period 1996 to 2000.[5]

Information from the National Cancer Data Base (NCDB) indicates that 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.[9] In 2006, approximately 1500 cancer deaths will occur among persons living with thyroid carcinoma in the United States.[6] Thyroid carcinoma occurs more often in women; however, mortality rates are higher for men, probably because they are usually older than women at the time of diagnosis.[5,10]

The incidence of thyroid carcinoma increased almost 240% between 1950 and 2000, but mortality rates decreased more than 44%.[5] From 1973 to 2002, thyroid cancer rates in the United States more than doubled. Because overall mortality has remained stable since 1973, the increasing incidence probably partially reflects earlier detection of subclinical disease (ie, small papillary cancers), although even microcarcinomas can metastasize regionally, thereby increasing eventual recurrence risk.[11,12] It is also notable that the stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates being observed with other solid tumors in adults.[6]

The Challenge of Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary and follicular) thyroid carcinoma can be a challenge, because no prospective randomized trials of treatment have been done. 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.[13] The treatment of choice is surgery, whenever possible, followed in many patients by radioiodine (^{131}I) and thyroxine therapy. External radiation therapy (RT) 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, usually causing papillary carcinoma. The thyroid glands of children are especially vulnerable to the carcinogenic action of ionizing radiation. A child's thyroid gland has one of the highest risks of developing cancer of any organ. In fact, the thyroid gland is the only organ linked to risk at about 0.10 Gy by convincing evidence.[3] The risk of radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma.[14] This suggests that genetic factors are also important in its development. Beginning within 5 years of irradiation, 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.[3,4]

Previously, most studies showed that ^{131}I is less effective than external gamma radiation in inducing thyroid carcinoma.[15] However, most of the studies that came to this conclusion involved adults, in whom the risk of developing thyroid carcinoma after exposure to ^{131}I appears to be small or nonexistent.[16] After the Chernobyl nuclear reactor accident in 1986, many children developed papillary thyroid carcinoma after being exposed to radioiodine fallout. It became evident that ^{131}I and other short-lived radioiodines were potent thyroid carcinogens in children, particularly those who were younger than 10 years when they were exposed.[17] Although radiation-induced papillary thyroid cancer tends to appear more aggressive histologically and to have high recurrence rates, the prognosis for survival is not clearly different from that of spontaneously occurring tumors.[18,19]

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary or follicular) thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. However, evaluating for malignancy is difficult, because benign nodules are so prevalent and thyroid carcinoma, by contrast, is so uncommon.[1] Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their cause. 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] 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.[10]

Factors Affecting Risk of Malignancy

Nodule size has a bearing on the risk of malignancy and the clinical evaluation. Thyroid nodules smaller than 1 cm occur with such frequency in the asymptomatic general population that they are found, in many cases, by serendipity when performing imaging studies for other head or neck problems. Often termed "incidentalomas," nodules smaller than 1 cm are almost invariably clinically benign lesions and usually do not require biopsy.[1,2,20] By contrast, nodules more than 4 cm in diameter are more suggestive and pose a somewhat higher risk of malignancy.

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.[21] For example, the likelihood that a nodule is malignant increases about seven-fold if it is very firm, fixed to adjacent structures, associated with enlarged regional lymph nodes, causes vocal cord paralysis, or is rapidly growing or if symptoms of invasion into neck structures are present.[21,22] If two or more of these features are present, the likelihood of thyroid cancer is virtually assured.[22]

A patient's age and gender also affect the probability of malignancy. The risk of malignancy is higher in patients younger than 15 years and older than 60 years. In particular, a man older than 60 years with a thyroid nodule has about four times the risk of having thyroid carcinoma than does a middle-aged woman with a thyroid nodule.[23] Other factors that increase the suspicion of malignancy include (1) a history of head and neck irradiation; (2) a family history of thyroid carcinoma; (3) the presence of familial syndromes associated with thyroid carcinoma (see "Familial Syndromes"); (4) evidence of other diseases associated with the multiple endocrine neoplasia type 2 syndromes (MEN 2), such as hyperparathyroidism, pheochromocytoma, a marfanoid habitus, or mucosal neuromas (MEN 2B); or (5) the presence of suspicious findings detected by ultrasound, such as central hypervascularity, irregular border, and/or microcalcifications.[24]

Initial Workup

Fine-needle aspiration (FNA) of the nodule or clinically suspicious lymph nodes is recommended as the first diagnostic test in a clinically euthyroid patient before any imaging studies are done.[1] Ideally, the serum thyrotropin (thyroid-stimulating hormone [TSH]) results should be known before FNA is performed. This is often impractical, however, and FNA may be done during the initial office visit. Some clinicians, especially in Europe,[25] recommend obtaining serum calcitonin levels from all patients with thyroid nodules, but this practice is probably not cost effective and has not been recommended by the American Thyroid Association.[26] Ultrasound of the thyroid and neck, including adjacent cervical lymph nodes, is also recommended.[27]

Cytologic examination of an FNA specimen, with sufficient cells recovered to assign a diagnosis, is typically categorized as (1) malignant; (2) suspicious for malignancy, including follicular neoplasms and Hürthle cell neoplasms; (3) benign (such as nodular goiter, hyperplastic nodule, or thyroiditis). Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in the diagnosis of thyroid disorders. Although FNA is a very sensitive test—particularly for papillary, medullary and anaplastic carcinomas—false-negative results are sometimes obtained; therefore, a reassuring FNA should not override concerns in the presence of worrisome clinical findings.[28] In contrast, FNA is far less able to discriminate follicular and Hürthle cell carcinomas from benign adenomas, because the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion. Nodules that yield an abundance of follicular cells with little or no colloid are nearly impossible to categorize as benign or malignant on the basis of FNA. Surgical biopsy is advisable, because approximately 20% of all such lesions are follicular carcinomas.[21]

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN thyroid panel is in favor of pathology synoptic reports from the (1) College of American Pathologists (CAP), and (2) the Association of Directors of Anatomic and Surgical Pathology (ADASP). Some pathologists currently use a modified format that is felt to comply with both of these synoptic reports. Although there is no published ADASP checklist for thyroid carcinoma, the CAP protocol information and checklists can be accessed at: http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, pathologists should familiarize themselves with these documents. The CAP protocols and ADASP checklists comply with the COC requirements.

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. Before thyroidectomy is performed, however, serum TSH level and thyroid ^{123}I or 99m technetium scanning may identify patients with an autonomously functioning or “hot” nodule who often may be spared surgery, because the diagnosis of follicular adenoma is highly likely.[29] Clinically euthyroid patients with a low TSH and a hot nodule on thyroid scan should be evaluated and treated for thyrotoxicosis as indicated even when cytology is suspicious for follicular neoplasm; those with a “cold” nodule should proceed to surgery. Those patients with a high or normal TSH and cytology suspicious for follicular or Hürthle cell neoplasm should undergo open biopsy with thyroidectomy. A trial of thyroxine therapy might be considered for a small, clinically nonsuspicious, follicular neoplasm in a young female patient, although the panel disagreed about this recommendation (category 3). If the patient receives thyroxine therapy, re-aspiration or surgery should be performed if the lesion grows.

Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of growth.[21] The use of thyroid hormone to suppress benign thyroid nodules is controversial, and additional clinical trials are necessary to guide management.[30,31] An FNA that yields insufficient cellular material for diagnosis should be repeated, because approximately 50% of subsequent specimens are adequate to assign a diagnosis.[21] In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.[32]

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 providing ample opportunity for cure. 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.

Prognosis and Recurrence of Differentiated Thyroid Carcinoma

In the NCDB study, the 10-year relative survival rates for patients with papillary, follicular, and Hürthle cell carcinomas were 93%, 85%, and 76%, respectively.[9] Although anaplastic thyroid carcinoma is uniformly lethal, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases.

Depending on initial therapy and other prognostic variables, about 30% of patients with differentiated thyroid carcinoma have tumor recurrences during several decades; 66% of these recurrences occur within the first decade after initial therapy.[10] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[33,34] 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% died of cancer.[10] 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.[10]

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular thyroid carcinomas, the two most important and consistently demonstrable are patient age at the time of initial therapy and tumor stage.[10,35-37] Age is the most important prognostic variable for thyroid cancer mortality. 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.[10,35-38] This disparity between cancer-related mortality and the frequency of tumor recurrence probably accounts for most of the profound disparity of opinion among clinicians concerning optimal treatment for patients with differentiated thyroid cancer. How clinicians assess the importance of tumor recurrence (as opposed to cancer-specific survival) accounts for much of the debate surrounding the influence of age on the treatment plan for children and young adults.

Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good.[39,40] One study found, however, that although the prognosis of children with thyroid carcinoma is favorable for long-term survival (90% at 20 years), the standardized mortality ratio was eight-fold higher than predicted.[41] Some authors believe that young age in a patient 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,[42-44] although 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.[10,39,45,46]

Prognosis is less favorable in men than in women, but the difference is usually small.[10,44] 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.[10] Because of this risk factor, men with thyroid carcinoma, especially those who are older than 40 years, should be regarded with special concern.

Familial Syndromes

Familial, nonmedullary thyroid carcinoma accounts for about 5% of papillary carcinomas and, in some cases, may be clinically more aggressive than the sporadic form.[47] One study found that microscopic familial papillary thyroid carcinoma tends to be multifocal and bilateral, often with vascular invasion, lymph node metastases, as well as high rates of recurrence and distant metastases.[48] Other familial syndromes associated with papillary thyroid carcinoma are Gardner's syndrome, familial adenomatous polyposis,[49] Carney complex (multiple neoplasia and lentiginosis syndrome which affects endocrine glands),[50] and Cowden's syndrome (multiple hamartomas).[51] The prognosis for all of these syndromes is not different from the prognosis of spontaneously occurring papillary thyroid carcinoma.

Tumor Variables Affecting Prognosis

Some tumor features have a profound influence on prognosis.[38,52-54] Perhaps the most important features are tumor histology, primary tumor size, local invasion, and metastases.

Histology

Although survival rates with typical papillary carcinoma are quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors.[1] A well-defined tumor capsule, which is found in about 10% of papillary thyroid carcinomas, is a particularly favorable prognostic indicator. A graver 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.[55] Follicular-variant papillary carcinoma, which is recognized by its follicular architecture and typical papillary cytology, does not appear to have a worse prognosis than the pure papillary lesions.[38,55,56]

Follicular carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It usually has a microfollicular histologic pattern. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.[57] Many follicular 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.[58] FNA or frozen section study cannot differentiate a minimally invasive follicular carcinoma from a follicular adenoma. Therefore, the tumor is often simply referred to as a "follicular neoplasm" by the cytopathologist. The diagnosis of cancer may be assigned only after thyroidectomy and indeed only after analysis of the "permanent" histologic sections shows tumor capsule invasion by follicular cells.

Highly invasive follicular 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 as many as 20% of patients, often within a few years of diagnosis.[38] The poor prognosis is closely related to the patient's older age at the time of diagnosis, advanced tumor stage, and larger tumor size.[10]

The mortality for papillary and follicular carcinomas is similar in patients of comparable age and disease stage. Both cancers have an excellent prognosis if the tumors are confined to the thyroid, are small, or are minimally invasive. Both papillary and follicular carcinomas have far less favorable outcomes if they are highly invasive or develop distant metastases.[10,59] Note that staging for patients with papillary and follicular carcinoma who are older than 45 years has been revised in the 2002 guidelines (6th edition) from the American Joint Commission on Cancer (AJCC) (see Table 1).[60] Many studies (including those discussed in this manuscript) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[61] and not the 6th edition.[60]

When Hürthle (oncocytic) cells constitute most or all of a malignant tumor's mass, the disease is often classified as Hürthle cell carcinoma, although the World Health Organization classification considers it as a variant of follicular carcinoma.[62] Molecular studies suggest, however, that this tumor may be more similar to papillary than follicular carcinomas.[63] 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.[64] Hürthle cell carcinomas may be aggressive and unpredictable with a mortality rate as high as 25% in 30 years when large tumors are identified in older patients.[65,66] Some believe these cancers are not much more aggressive than similarly staged follicular carcinomas without Hürthle cells.[67] In the NCDB report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.[9]

In two large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, about twice the frequency of follicular carcinoma metastases.[68,69] Fewer Hürthle cell carcinomas concentrate ^{131}I than do papillary or follicular carcinomas. The University of Texas M. D. Anderson Cancer Center reported that in a series of 100 patients with distant metastases, ^{131}I uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell carcinomas.[70]

Primary Tumor Size

Papillary carcinomas smaller than 1 cm, termed "*microcarcinomas*," are typically found incidentally after surgery for benign thyroid conditions. Their recurrence and cancer-specific mortality rates are near zero.[71,72]

Other small papillary carcinomas 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,[73] which may be the presenting feature and also may be associated with distant metastases.[72] Otherwise, small (< 1.5 cm) papillary or follicular carcinomas confined to the thyroid almost never cause distant metastases. Furthermore, rates of recurrence 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.[10] In fact, the prognosis for papillary and follicular carcinomas is incrementally poorer as tumors increase in size.[59,74] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas (see Figure 2).[10]

Local Tumor Invasion

Up to 10% of differentiated thyroid carcinomas invade through the outer border of the gland and grow directly into surrounding tissues, increasing both morbidity and mortality. The local invasion may be microscopic or gross; it can occur with both papillary and follicular carcinomas.[10,75] Recurrence rates are two times higher with locally invasive tumors, and as many as 33% of patients with such tumors die of cancer within a decade.[10,76]

Lymph Node Metastases

In one review, nodal metastases were found in 36% of 8029 adults with papillary carcinoma, in 17% of 1540 patients with follicular carcinoma, and in up to 80% of children with papillary carcinoma.[38] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[77] The prognostic importance of regional lymph node metastases is controversial. Some studies find that the presence of regional lymph node metastases has no effect on recurrence or survival.[42-44] Other studies find that nodal metastases are a risk factor for local tumor recurrence as well as cancer-specific mortality and that nodal metastases correlate with distant metastases, especially if there are bilateral cervical or mediastinal lymph node metastases or if the tumor invades through the lymph node capsule.[10,37,78] In one study, 15% of patients with cervical node metastases died of thyroid carcinoma (P<.02), whereas all patients without cervical node metastases survived.[79] Another study of patients with distant metastases from papillary carcinoma reported that 80% had mediastinal node metastases at the time cancer was diagnosed.[80] Still another study found that patients with papillary or follicular carcinoma who had cervical or mediastinal lymph node metastases had a significantly (P<.01) higher 30-year cancer-specific mortality (10%) than patients without metastases (6%).[10]

Distant Metastases

Distant metastases are the principal cause of death from papillary and follicular carcinomas. Almost 10% of patients with papillary carcinoma and up to 25% of those with follicular carcinoma develop distant metastases. About 50% of these metastases are present at the time of diagnosis.[38] Distant metastases occur even more often in patients with Hürthle cell cancer (35%) and in those patients diagnosed after age 40 years.[68,70] The sites of reported distant metastases among ^{123}1 patients in 13 studies were lung (49%), bone (25%), both lung and bone (15%), and the central nervous system (CNS) or other soft tissues (10%).[38] The main predictors of outcome for patients with distant metastases are patient's age, the tumor's metastatic site, ability to concentrate ^{131}I, and morphology on chest radiograph.[68,70,81,82]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[38] 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.[83] The survival rates are highest in young patients with diffuse lung metastases seen only on ^{131}I imaging and not on x-ray,[82,83] which appears to be the most important feature governing an improved survival rate and prolonged disease-free interval with lung metastases.[84] Prognosis is worse with large pulmonary metastases that do not concentrate ^{131}I and is intermediate with small nodular metastases that are seen on radiographs but that do concentrate ^{131}I.[68,70,81]

Tumor Staging and 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.[36,42,60,85] When applied to the papillary carcinoma data from the Mayo Clinic, four of the schemes using age (EORTC [European Organization for Research and Treatment of Cancer], TNM 5th edition [tumor, node, metastasis], AMES [Age, Metastases, Extent, and Size], and AGES [Age, tumor Grade, Extent, and Size]) were effective in separating low-risk patients (in whom the 20-year, cancer-specific mortality was 1%) from high-risk patients (in whom the 20-year, cancer-specific mortality was 30% to 40%).[74] 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%, 56%, and 24%, respectively.[42] It is noteworthy that only "Completeness of resection" is subject to intervention, and its contribution to prognosis is small.

Unfortunately, a study that classified 269 patients with papillary carcinoma according to five different prognostic paradigms found that some patients in the lowest risk group from each approach died of cancer.[45] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[60,86] 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,[87,88] TNM staging was not established as a predictor of recurrence and therefore does not forecast accurately the recurrences that often occur in patients who develop thyroid cancer when they are young. Currently, no prognostic systems address variants of papillary and follicular carcinoma whose clinical behavior affects outcome. Two studies have demonstrated the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.[36,89]

Differentiated thyroid cancer staging systems are certainly of value in epidemiology studies and as tools to stratify patients for prospective trials.[90] Staging systems, which are designed to segregate patients on the basis of survival, offer gross indications of prognosis for groups of patients but probably are of far less utility in determining treatment for individual patients. When treating differentiated thyroid cancer, where most patients do not succumb to cancer, many clinicians have placed a stronger emphasis on potential morbidity than on mortality.

Systems designed to predict survival provide little guidance with respect to morbidity sustained by patients who are likely to be cured by their treatments. Although the TNM classification of the AJCC and International Union Against Cancer (UICC) is universally available and widely accepted for other disease sites, the NCCN Thyroid Carcinoma Guidelines 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. Several international surveys, including one by the clinical members of the American Thyroid Association, indicate that most clinicians do not factor age into their therapeutic decisions.[91,93] This view is held by most participants in this NCCN Thyroid Carcinoma Panel.

Surgical Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total or Near-Total Thyroidectomy

The continuing debate surrounding the appropriate extent of thyroid resection reflects the limitations of prognostic scoring[44] and the morbidity often associated with total thyroidectomy performed outside of referral centers. For example, Hay and colleagues reported in 1987 that patients treated at the Mayo Clinic for low-risk papillary thyroid carcinomas (MACIS score 3.99 or less) had no improvement in survival rates after undergoing procedures more extensive than ipsilateral lobectomy and, accordingly, concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[94] In 1998, however, that center reported the results of a study designed to compare cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy. The study involved patients with papillary carcinoma considered to be low risk by AMES criteria.[95] The investigators found no significant differences in cancer-specific mortality or distant metastasis rates between the two groups, but 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. On the basis of these observations, Hay and colleagues concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk papillary carcinoma.[95]

Most NCCN panel members (and other authors) advise total or near-total thyroidectomy for all patients in whom the diagnosis of thyroid carcinoma is assigned preoperatively,[13,96,98] because, while they have little influence on deaths from cancer, such procedures are associated with improved disease-free survival, even in children and adults with low-risk tumors.[33,46,95,99] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe[38,94] with an overall long-term recurrence rate of more than 30% (versus 1% after total thyroidectomy and ^{131}I therapy)[10] and the highest frequency (11%) of subsequent pulmonary metastases.[100] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for more complete initial thyroid resection.[10] However, some prominent thyroid cancer specialists (including some at NCCN institutions) oppose this view and advocate unilateral lobectomy for most patients with papillary and follicular thyroid carcinoma on the basis of both the low mortality among those patients categorized as low risk by the AMES and other prognostic classification schemes (ie, most patients) and of the high complication rates reported with more extensive thyroidectomy.[43,85,101] The large thyroid remnant, however, may complicate long-term follow-up with serum thyroglobulin (Tg) determinations, and it will frustrate whole-body ^{131}I scans. In most clinical settings, decisions surrounding the extent of thyroidectomy should be individualized and undertaken in consultation with the patient. Circumstances in which unilateral thyroidectomy is inadvisable are detailed in the guidelines.

NCCN panelists 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.[10,71,72] The same is true for minimally invasive follicular cancers smaller than 4 cm.

Completion Thyroidectomy

This procedure is recommended when long-term follow-up with serum Tg determinations and whole-body ^{131}I scans are planned. Large thyroid remnants are difficult to ablate with ^{131}I.[100] Completion thyroidectomy has a comparable net complication rate to that of total thyroidectomy. Some oncologists 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.[75,102-106] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[104]

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.[46] 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.[105]

Surgical Complications

The most feared complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury. These complications occur with much higher frequency after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults[107] and still more common in children[46,108] undergoing total thyroidectomy. However, the rates of persistent hypocalcemia are reported to be much lower, at least in the hands of experienced thyroid surgeons. In a review of seven published surgical series, the average 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.[109] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[110]

When experienced surgeons perform the operations, complications occur at a lower rate. A study of 5860 patients treated in the state of Maryland found that surgeons who performed more than 100 thyroidectomies a year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies a year had four times as many complications.[111]

Radioactive Iodine

Adjuvant Radioiodine Therapy

Postoperative ^{131}I thyroid remnant ablation is performed when the patient has a tumor with the potential for recurrence.[112] Studies demonstrate decreased recurrence and disease-specific mortality when postoperative ^{131}I therapy is administered as part of the initial treatment, but the supportive data are largely confined to higher risk populations.[10,37,45,113,114] In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was about three-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 ^{131}I (P<.001). Moreover, fewer patients developed distant metastases (P<.002) after thyroid remnant ^{131}I ablation than after other forms of postoperative treatment; however, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter.[113] Some find that remnant ablation has less of a therapeutic effect, perhaps, because more extensive thyroidectomy had been done.[74]

Debate continues about ablating the thyroid bed with ^{131}I after near-total thyroidectomy.[74,113] Proposed mechanisms by which remnant ablation may decrease recurrences and disease-specific mortality include the ablation of normal tissue destined to become malignant, ablation of residual microscopic malignancy in the remnant, ablation of residual microscopic malignancy outside the remnant, ablation of residual malignancy outside the remnant obscured by uptake in a large thyroid remnant, and the demonstration of unsuspected residual malignancy on the post-therapy scan, which alters disease stage and promotes further patient management. Other reasons favoring remnant ablation include (1) simplified patient follow-up, because elimination of “thyroid bed” uptake eliminates misinterpretation of it as disease; (2) remnant ablation eliminates 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. However, long-term evaluation of recurrence risk after adjuvant radioiodine may be confounded by the accompanying improved specificity of diagnostic testing after elimination of the thyroid remnant, as well as the possibility that patients who receive adjuvant therapy may be more likely to undergo more intensive follow-up testing.

Diagnostic Whole-Body Scans and Thyroid Stunning

Whole-body ^{131}I scans are often performed after surgery to assess the completeness of thyroidectomy and the presence of residual disease. However, a phenomenon termed “stunning” may occur when scanning doses of ^{131}I induce follicular cell damage. Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent ^{131}I.[115]

The use of ^{123}I or small (2 or 3 mCi) doses of ^{131}I and/or a shortened interval of not more than 72 hours between the diagnostic ^{131}I dose and the therapy dose has been recommended to avoid or reduce the stunning effect; however ^{123}I is more expensive and smaller ^{131}I doses have reduced sensitivity when compared with larger ^{131}I doses.[115,116] Some experts recommend that diagnostic ^{131}I scans be avoided completely with decisions based on the combination of tumor stage and serum Tg. Other experts advocate that the whole-body ^{131}I diagnostic scan 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 radioiodine dosage to avoid substantial radiation thyroiditis.[117]

Administration of Radioiodine Therapy

Three methods of determining ^{131}I therapy activities (doses) include: empiric fixed doses, quantitative dosimetry, and upper bound limits that are set by blood dosimetry.[118] In the past, hospitalization was required to administer therapeutic doses of ^{131}I larger 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 ^{131}I doses in ambulatory patients.[118]

Fixed ^{131}I Doses

Administration of a fixed dose of ^{131}I is the most widely used and simplest method. Most clinics use this method regardless of the percentage uptake of ^{131}I in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of ^{131}I. Lymph node metastases that are not large enough to excise are treated with about 100 to 175 mCi (3700 to 6475 MBq) of ^{131}I. 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 ^{131}I, which typically will not induce radiation sickness or produce serious damage to other structures. Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of ^{131}I (which is very uncommon) are treated with 150 mCi of ^{131}I (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.

Quantitative Tumor ^{131}I Dosimetry

A second method is to use quantitative dosimetry methods to estimate the amount of radiation delivered to the lesion per unit of ^{131}I administered. Some oncologists favor this approach, because radiation exposure from arbitrarily fixed doses of ^{131}I can vary substantially. If the calculated dose to the tumor is less than 3500 cGy, it is unlikely that the cancer will respond to ^{131}I therapy.[118,119] Radioiodine activities that deliver more than 30,000 cGy to the residual normal tissue and more than 8000 cGy to metastatic foci are likely to be effective. It is necessary to serially measure the radiation activity in the target using a tracer dose and to estimate the tumor size to make these calculations, which is difficult to do and is impossible in the setting of diffuse or microscopic lung metastases.

Blood ^{131}I Dosimetry

A third method is to administer a dose calculated to deliver a maximum of 200 cGy to the blood, while keeping the whole-body retention less than 120 mCi (4440 MBq) at 48 hours or less than 80 mCi (2960 MBq) when there is diffuse pulmonary uptake.[120] Thyroid cancer dosimetry and radioiodine therapy with doses above 200 mCi are best done in medical centers with experience using these treatments.

Post-Treatment ^{131}I Scans

When ^{131}I therapy is given, a whole-body scan should be performed to document ^{131}I uptake by the tumor. The whole-body scan should be done primarily, because up to 25% of post-treatment scans show lesions that may be clinically important that were not detected by the diagnostic scan.[118] In a study of pretreatment and post-treatment scans, the two differed in 27% of the treatment cycles, but only 10% of the post-treatment scans showed clinically significant new foci of metastatic disease.[121] Post-treatment scans were most likely to reveal clinically important new information in patients younger than 45 years who had received ^{131}I therapy in the past. Conversely, in older patients and patients who had not previously received ^{131}I therapy, the post-treatment scans rarely yielded new information that might have altered the patient's prognosis.[121]

Assessment and Management After Initial Treatment

Serum Tg determinations and whole-body ^{131}I imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation. In contrast, neither study is specific for patients who have undergone lobectomy. When initial ablative therapy has been completed, serum Tg should be measured periodically; whole-body ^{131}I scanning should be done after thyroxine therapy is discontinued or recombinant human TSH (rh-TSH) is administered. Serum Tg can be measured while the patient is taking thyroxine, but the test is more sensitive when thyroxine has been stopped or when rh-TSH is given to increase the serum TSH.[122,123] 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, although 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 required to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements and ^{131}I scanning can be performed to detect residual thyroid tissue or carcinoma. An alternative to thyroid hormone withdrawal is the administration of rh-TSH intramuscularly, which stimulates thyroidal ^{131}I uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.[124]

The drug has been approved for diagnostic use and has been tested in two large international multicenter studies. The first study found that whole-body ^{131}I scans were of good quality for patients who received two 0.9-mg doses of rh-TSH while continuing thyroid hormone. The results were equivalent to those for scans obtained after withdrawing thyroid hormone in 66% of the patients, superior in 5% of patients, and inferior in 29%. This study proved that rh-TSH stimulates ^{131}I uptake for whole-body scanning but that the sensitivity of ^{131}I scanning after rh-TSH administration was less than after the withdrawal of thyroid hormone.[124]

A second multicenter international study was performed to assess the effects of two rh-TSH dosing schedules on whole-body ^{131}I scans and serum Tg levels when compared with scans and Tg levels obtained after thyroid hormone withdrawal. The scanning method in this study was more carefully standardized and took into account the fact that ^{131}I retention was higher in patients rendered hypothyroid than in patients given rh-TSH.[123] Scans were concordant in 89% of the patients and superior in 4% of the patients after rh-TSH and superior in 8% of patients after thyroid hormone withdrawal, but these differences were not statistically significant. The main finding in this study was that the combination of rh-TSH–stimulated whole-body scanning and serum Tg measurements detected 100% of metastatic carcinoma.[123] In this study, 0.9 mg of rh-TSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of ^{131}I on the third day. A whole-body scan and Tg measurements were performed on the fifth day. Whole-body ^{131}I images were acquired after 30 minutes of scanning 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 rh-TSH injection indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole-body scan findings.[123,125]

This drug is well tolerated. Nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[123] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[124]

Measuring Serum Tg

Serum Tg measurement is the best means of detecting thyroid tissue. Tg should be measured when TSH has been stimulated by thyroid hormone withdrawal or rh-TSH, when serum Tg has a lower false-negative rate than whole-body ^{131}I scanning.[122,123] The sensitivity and specificity of various Tg assays, however, vary widely in different laboratories, even with the use of an international standard (CRM 457).[126] It is therefore 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.

Although there are no other known sources of Tg to falsely increase levels, anti-Tg antibodies should be measured in the serum sample taken for Tg assay, because these antibodies (which are found in up to 25% of patients with thyroid carcinoma) invalidate serum Tg measurements in most assays.[127] These antibodies typically falsely lower the Tg value in immunochemiluminometric assay (ICMA) and immunoradiometric (IRMA) assays, while raising the value in older radioimmunoassay (RIA). Although the clinical importance of these antibodies is unclear, their persistence for more than 1 year after thyroidectomy and radioiodine ablation probably indicates the presence of residual thyroid tissue and possibly an increased risk of recurrence.[127] In one study, 49% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of 100 U/mL or more had a recurrence when compared with only 3% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of less than 100 U/mL.[128] In patients with co-existent 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.[129] RNA-based detection strategies (including the sodium-iodine symporter [NIS], TSH receptor, and Tg mRNAs) or DNA-based strategies to detect thyroid oncogenes in peripheral blood, represent current areas of active research that may improve the detection of residual cancer and the monitoring of these patients, especially during thyroxine treatment or when circulating anti-Tg antibodies are present.[130,131]

Treating Tg-Positive/Scan-Negative Patients

Post-treatment ^{131}I scans are most likely to yield localizing information when the serum Tg level is increased, but a tumor cannot be found by physical examination or localizing techniques (such as diagnostic ^{131}I scans, neck ultrasonography, computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET]). Pulmonary metastases may be found only after administering therapeutic doses of ^{131}I and obtaining a whole-body scan within a few days of treatment.[132] In a study of 283 patients treated with 100 mCi (3700 MBq) of ^{131}I, 6.4% had lung and bone metastases detected after treatment that had been suspected on the basis of high serum Tg concentrations alone but had not been detected after 2-mCi (74 MBq) diagnostic scans.[133]

In another study, all but 1 of 17 patients with increased serum Tg concentrations and negative 5-mCi (185 MBq) diagnostic scans showed ^{131}I uptake after 75 to 140 mCi (2775 to 5180 MBq) of ^{131}I; more than 50% of these patients had lung metastases.[134] Unfortunately, most diagnostic scan–negative/Tg-positive patients are not rendered disease free by ^{131}I therapy; however, the tumor burden may be diminished.[135] Patients not benefiting from this therapy can be considered for clinical trials. A phase II, multicenter clinical trial is underway testing the hypothesis that an inhibitor of DNA methylation, decitabine, can induce radioiodine-concentrating ability in metastatic disease not evident on diagnostic scans. Nevertheless, patients without bulky residual disease may have prolonged survival without clinical recurrence; therefore, their need for antineoplastic therapy remains uncertain. When a large tumor is not visible on a diagnostic whole-body scan, this implies that its ^{131}I concentrating ability per gram of tissue is very low and hence a lack of response to ^{131}I therapy may be anticipated.

The Tg level recommended for treatment has been decreasing; it was approximately 30 or 40 ng/mL about a decade ago, but now it is approximately 10 ng/mL.[132,136] However, no study has yet demonstrated any decrease in morbidity or mortality in patients treated with ^{131}I on the basis of increased Tg measurements alone. In a long-term follow-up study, no suggestion of a survival advantage was associated with empiric high-dose radioiodine in scan-negative patients.[137] Further, potential long-term side effects (such as xerostomia, nasolacrimal duct stenosis, bone marrow and gonadal compromise, and the risk of hematologic and other malignancies) may negate any benefit.[112,138]

Thyroid Hormone Suppression of TSH

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma are reported by some authors for patients treated with thyroid hormone suppressive therapy.[10,113,139-141] The average dosage needed to attain serum TSH levels in the euthyroid range is higher in patients with thyroid carcinoma (2.11 mcg/kg per day) than in those patients with spontaneously occurring primary hypothyroidism (1.62 mcg/kg per day)[142] and still higher doses are required to suppress serum TSH in thyroid carcinoma patients. Still, the optimal TSH level to be achieved in patients with thyroid carcinoma is uncertain. A French study found that a constantly suppressed TSH level (0.05 mU/mL or less) was associated with a longer relapse-free survival when compared with serum TSH levels that were always 1 mU/mL or higher; furthermore, the degree of TSH suppression was an independent predictor of recurrence.[140] A prospective U.S. study of 617 patients by the National Thyroid Cancer Treatment Cooperative Study Group found that greater TSH suppression possibly improved progression-free survival in high-risk stage III and stage IV patients but did not improve survival in low-risk stage I and II patients.[141] These data do not support the concept that excessive TSH suppression (into the undetectable, thyrotoxic range) is required to prevent disease progression in all patients with differentiated thyroid cancer. As a practical matter, the most appropriate dose of thyroid hormone for most low-risk patients with differentiated thyroid carcinoma is the dose that decreases the serum concentration to just below the lower limit of the normal range for the assay being used. A greater degree of suppression is generally recommended for higher risk patients.

Adjuvant External Radiation Therapy

No prospective controlled trials have been completed using adjuvant external RT. An attempt to perform such a study encountered marked resistance to randomization among most patients eligible to participate in such a trial.[143] One retrospective study demonstrated a benefit of adjuvant external RT after radioactive iodine in patients older than 40 years who have invasive papillary thyroid cancer (T4) and lymph node involvement (N1).[144] Local recurrence as well as locoregional and distant failure were significantly improved. A second study demonstrated improved cause-specific survival and local relapse-free rate in selected patients treated with adjuvant external RT (in addition to total thyroidectomy and TSH-suppressive therapy with thyroid hormone) for papillary thyroid carcinoma with microscopic residuum. Not all patients received radioactive iodine therapy.[37] Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of papillary thyroid carcinoma. Patients with microscopic residual papillary carcinoma after surgery are more commonly rendered disease free after receiving external RT (90%) than when not receiving it (26%).[145] Patients with microscopically invasive follicular carcinoma after surgery are also more often disease free when postoperative external RT is given (53%) than when it is not given (38%).[145] However, these patients had not received radioactive iodine. Similar benefit was shown with radioactive iodine alone in comparable patients treated with radioactive iodine after surgery.[145]

Chemotherapy, External Radiation, and Surgical Excision of Metastases

Focal lesions that do not concentrate ^{131}I adequately and isolated skeletal metastases should be considered for surgical excision or external irradiation. Brain metastases pose a special problem, because ^{131}I therapy may induce cerebral edema. 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.[146]

Life-threatening tumors refractory to all other forms of therapy may be palliatively treated with doxorubicin, although the response rate is poor.[38] The experience with chemotherapy in patients with differentiated thyroid carcinoma is limited, because most recurrent tumors respond well to surgery, ^{131}I therapy, or external-beam RT. Chemotherapy's main use is for tumors that are not surgically resectable, are not responsive to ^{131}I, and have either been treated with or are not amenable to therapy with external-beam RT. Among 49 patients with metastatic differentiated thyroid carcinoma who were treated with five chemotherapy protocols, only two (3%) patients had objective responses.[147] In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.[148] Combination chemotherapy is not clearly superior to doxorubicin therapy alone.[38]

Recently, a broad variety of phase II trials have been initiated to evaluate novel treatments for patients with metastatic differentiated thyroid carcinoma. The first to be completed and published was a phase II study of celecoxib (400 mg twice daily) in patients with progressive, radioiodine-unresponsive disease.[149] Although 12-month progression-free survival was only 3%, 38% of the patients had stable disease, representing an alteration in their disease course. Currently, multiple other agents are in phase II trials, including the (1) multi-targeted kinase inhibitors, such as AMG-706, sorafenib, and axitinib; (2) histone deacetylase inhibitors, SAHA and depsipeptide; (3) DNA methylation inhibitor, decitabine; (4) HSP-90 inhibitor, 17-AAG; and (5) proteasome inhibitor, bortezomib.

Papillary Thyroid Carcinoma

Surgical Therapy

A CT/MRI should be performed if the lesion is fixed or substernal (iodinated contrast should be avoided unless essential). A thyroid and neck ultrasound are recommended if not previously done. 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.[150] The recommendation from the guidelines panel to evaluate vocal cord mobility was one of nonuniform consensus (category 2B). A chest x-ray can be considered.

The panel members agreed on the characteristics of patients who require total thyroidectomy and neck dissection (if nodes are positive) as the primary treatment. However, there was not uniform consensus about the preferred primary surgery for patients who are assumed to be at lower risk of cancer-specific mortality. The majority of panel members opted for total thyroidectomy (category 2B) in any patient in whom papillary thyroid carcinoma was identified preoperatively or at the time of surgery. However, a minority of panel members felt strongly that, initially, lobectomy plus isthmusectomy (category 2B) is adequate surgery for patients at lower risk. A recent 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.[151] For patients who undergo lobectomy plus isthmusectomy (lower risk patients), aggressive variant disease, macroscopic multifocal disease, positive margins, or cervical lymph node metastases warrant completion of thyroidectomy. Note that *aggressive variant disease* is defined as tall cell, columnar cell, insular, oxyphilic, or poorly differentiated features.

The panel agreed that completion of thyroidectomy is appropriate for any large tumor (>4 cm) with positive margins or for gross extrathyroidal invasion (T3 or T4). Incidentally discovered papillary carcinomas 1 cm or more in size may warrant a completion thyroidectomy (category 2B) for a clinically suspicious lymph node, contralateral lesion, or perithyroidal node, an aggressive variant, or macroscopic multifocal disease. Tg measurement plus anti-Tg antibodies is an alternative option to completion thyroidectomy. Lobectomy is sufficient for tumors resected with negative margins, no contralateral lesion, no suspicious lymph node, or small (<1 cm) papillary carcinomas found incidentally on the final pathology sections in the course of thyroid surgery for benign disease; Tg measurement plus anti-Tg antibodies may also be considered for surveillance for tumors with these features. Thyroxine therapy to reduce serum TSH to low or low normal concentrations should also be considered in these patients.

Radioactive Iodine

Postoperative Whole-Body ^{131}I Diagnostic Scans

Performing a diagnostic whole-body ^{131}I scan before ^{131}I therapy is a category 2B recommendation. The panel advises that this decision should be weighed against the problem of stunning that occurs with diagnostic ^{131}I scans.[152] A diagnostic whole-body ^{123}I scan does not carry a risk of stunning. The alternatives to performing a diagnostic ^{131}I scan are to obtain an ^{123}I scan before ^{131}I therapy or a whole-body scan a few days after treatment with ^{131}I, termed a “post-treatment ^{131}I scan” in the guidelines. If radioiodine is administered after a diagnostic ^{131}I study, the time interval between radioiodine doses should be minimized.

Thyroid Remnant Ablation With Radioactive Iodine

The decision to ablate uptake in the thyroid bed is closely linked to the extent of thyroid surgery and is not recommended for patients who have undergone lobectomy or lobectomy plus isthmusectomy as initial surgery. Although panel members debated about the use of ^{131}I to ablate uptake in the thyroid bed after total thyroidectomy, the guidelines recommend (category 2B) adjuvant radioiodine ablation if the patient has undergone total thyroidectomy and if the thyroid bed is positive on a radioiodine scan. Empiric administration of radioiodine without a diagnostic scan is not routinely recommended by the panel. In patients with detectable Tg but at levels of either 1-10 ng/mL or more than 10 ng/mL who are not receiving thyroid hormone and who have negative radioiodine scans, consideration of radioiodine therapy with a post-treatment scan is recommended, although there was major disagreement among panel members (category 3).[153]

Radioactive Iodine Treatment

Therapy with ^{131}I is advised for patients with tumors found on examination, imaging studies, or by increased serum Tg levels if these tumors are not amenable to surgical removal and if they concentrate ^{131}I. The postsurgical therapy recommendations include five options, based on serum Tg level and the results of a whole-body ^{131}I scan, as well as the general level of agreement among the panel members for ^{131}I treatment recommendations. For patients with both increased Tg levels (either Tg greater than 10 ng/mL or a Tg level 1-10 ng/mL) and a negative whole-body scan, ^{131}I treatment and a post-treatment ^{131}I scan should be considered (category 3). For patients with a metastatic site that is positive on a radioiodine scan, the panel recommends ^{131}I treatment and a post-treatment ^{131}I scan; however, it is assumed that palpable neck disease would be surgically resected before any radioiodine treatment. A third group of patients includes those with a positive thyroid bed on radioiodine scan; the panel recommended further radioiodine therapy (category 2B) and a post-treatment scan for these patients as previously discussed. The panel agrees that for patients with Tg levels less than 1 ng/mL and negative radioiodine scans, radioiodine treatment is not needed. The doses of ^{131}I are not specified in the guidelines except when recurrent disease is suspected on the basis of a high serum Tg values (more than 10 ng/mL) off thyroid hormone and negative imaging studies. In this setting, an empiric fixed dose of 100 to 150 mCi of ^{131}I can be considered. Although there was major disagreement, the guidelines recommend (category 3) that post-treatment whole-body scans be performed to assess the concentration of the isotope in tumor foci and to identify new areas of tumor growth not seen on diagnostic scans after ^{131}I therapy is administered.

Adjuvant External Radiation Therapy

The guidelines recommend that external RT be considered for patients older than 45 years with T4a (surgically evident extra-thyroidal invasion) and without gross residual disease in their neck.

Thyroxine Suppression of TSH

Thyroxine therapy is required after total thyroid resection, and it is advisable even after lobectomy and isthmusectomy. The level of TSH suppression is not stipulated, because data are conflicting on this point. As a practical matter, the most appropriate dose of thyroid hormone for most low-risk patients with differentiated thyroid cancer is a dose that decreases the serum TSH concentration to just below the lower limit of the normal range. At a minimum, patients should not be permitted to have increased TSH levels, because this would represent inadequate treatment of both postsurgical hypothyroidism and differentiated thyroid carcinoma. A greater degree of TSH suppression is generally recommended for higher risk patients.

Surveillance and Maintenance

Note that patients should receive at least one follow-up radioiodine scan if they have distant metastases and/or positive cervical nodes. Low-risk, stage I, and II patients no longer require routine radioiodine scans if they have negative stimulated Tg, negative neck ultrasound, and no longer have clinical disease and/or have had a negative radioiodine scan. The guidelines recommend the following: (1) long-term surveillance and maintenance with a physical examination, TSH and Tg measurements with anti-Tg antibodies every 6 to 12 months, then annually if patients remain disease free; (2) periodic neck ultrasound; (3) rh-TSH–stimulated Tg in low-risk patients with recent negative neck ultrasound and with negative TSH-suppressed Tg without distant metastases or soft tissue invasion on initial staging; (4) regular diagnostic whole-body ^{131}I scans every 12 months until absence of treatable disease (either withdrawal of thyroid hormone or rh-TSH) for patients with detectable Tg, distant metastases, or soft tissue invasion on initial staging; and (5) consider additional nonradioiodine imaging (eg, FDG PET with or without CT if Tg levels are 10 ng/mL or more) for patients whose ^{131}I scans are negative and stimulated Tg is increased more than 2 to 5 ng/mL. The panel acknowledges that the suggested Tg cutoff levels will continue to evolve as new Tg assays are introduced.

The serum Tg levels recommended in the guidelines show different cutoff points in response to the increase in serum TSH after thyroid hormone withdrawal or rh-TSH stimulation. Serum Tg generally does not rise as high after rhTSH as after withdrawal of thyroid hormone; therefore, the Tg cutoff points are lower after rh-TSH stimulation than after thyroid hormone withdrawal. The conditions for rh-TSH–stimulated whole-body ^{131}I scans stipulate using 4-mCi ^{131}I doses (based on the doses used in the pivotal phase III trial)[123] and a scanning time of 30 minutes or until 140,000 counts are obtained.

Recurrent Disease

The panel agrees that the preferred therapy for recurrent disease is surgery if the tumor can be localized and is resectable. For locoregional recurrences that are not amenable to surgery, ^{131}I therapy combined with external-beam RT is recommended for tumors that concentrate ^{131}I and external-beam RT alone is recommended for those that do not concentrate ^{131}I. For metastatic disease, several therapeutic approaches are recommended, depending on the site and number of tumor foci. For skeletal metastases, surgical palliation is recommended for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are ^{131}I treatment (if the whole-body scan is positive) and/or external-beam RT. Intravenous bisphosphonate (pamidronate or zoledronic acid) therapy may be considered for symptomatic bone metastases; embolization of metastases can also be considered.[154] For solitary metastases to the CNS, neurosurgical resection should be considered for appropriate cases, and/or radioiodine treatment (with rh-TSH and steroid prophylaxis) if the radioiodine scan is positive, and/or external-beam RT. For other extracervical sites, surgical resection of selected, enlarging, or symptomatic metastases can be considered; for other disseminated tumors, ^{131}I is recommended if the tumor concentrates the radioisotope (with consideration of dosimetry to maximize the dosing), or systemic chemotherapy if the patient is not in a clinical trial.[155] Because chemotherapy has been generally disappointing, the guidelines recommend clinical trials for tumors that do not concentrate ^{131}I.[96] The panel did not recommend any specific trials, because there are different options for each patient.

Follicular Thyroid Carcinoma

Because the diagnosis and treatment of papillary and follicular carcinoma are similar, only the important differences in the management of follicular carcinoma are highlighted. FNA is not as specific for follicular thyroid carcinoma as it is for papillary carcinoma and accounts for the main differences in management of the two tumor types. The FNA cytologic diagnosis of “follicular neoplasm” will prove to be a benign follicular adenoma in 80% of cases. However, 20% of patients with “follicular neoplasms” 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. The diagnosis of follicular carcinoma requires evidence for transcapsular nodule invasion or vascular invasion. Because most patients with “follicular neoplasms” 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 if cancer is found at pathologic review. Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery. If invasive follicular carcinoma (extensive vascular invasion) is found on the final histologic sections after lobectomy plus isthmusectomy, prompt completion of thyroidectomy is recommended.

Completion thyroidectomy should be considered for tumors that, on final histologic sections after lobectomy plus isthmusectomy, are minimally invasive follicular 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.[156] These tumors may also be simply followed carefully, because minimally invasive follicular carcinomas have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma do occasionally occur. The other features of management and follow-up for follicular carcinoma are identical to those of papillary carcinoma with the exception that adjuvant RT is not used as an adjuvant measure postoperatively for advanced lesions (ie, T4a). However, RT is used for nonresectable growing disease in the neck. Adjuvant radioiodine ablation of the thyroid bed (category 2B) (or radioiodine treatment) and post-treatment scan may be administered as is done for papillary carcinoma. The decision to perform a diagnostic whole-body ^{131}I scan before ^{131}I therapy is administered is a category 2B recommendation for both follicular and papillary carcinoma.

Hürthle Cell Carcinoma

This tumor (also known as oxyphilic cell carcinoma) is usually assumed to be a variant of follicular thyroid carcinoma, although the prognosis of Hürthle cell carcinoma is worse. The Hürthle cell variant of papillary carcinoma is rare and seems to have a prognosis similar to follicular thyroid carcinoma.[157] The management of this Hürthle cell carcinoma is almost identical to follicular carcinoma, except that (1) locoregional nodal metastases occur frequently; and (2) metastatic Hürthle cell tumors are less likely to concentrate ^{131}I. Adjuvant RT can be considered postoperatively for advanced Hürthle lesions (ie, T4a), similar to the management for papillary carcinoma. Nonetheless, adjuvant radioiodine therapy has been reported to decrease the risk of locoregional recurrence and should be considered after thyroidectomy for patients with Tg levels of either 1-10 ng/mL or more than 10 ng/mL who are also off thyroid hormone and radioiodine scan negative.[66] The panel recommends (category 2B) that a diagnostic whole-body ^{131}I scan be performed before ^{131}I therapy is administered. Cervical nodal metastases are also more common than in follicular carcinoma, and therefore regional nodal dissections may be appropriate in the presence of disease. Postoperative RT may be used for advanced lesions.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) derives from the neuroendocrine parafollicular or C cells of the thyroid.[158] Sporadic MTC accounts for 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, or familial MTC. 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.[159]

Symptoms from distant metastases in lungs or bones occur in 5% to 10% of patients. The ability of the tumor to secrete measurable quantities of calcitonin, occasionally along with other hormonally active peptides (such as adrenocorticotrophic hormone [ACTH] or calcitonin-gene related peptide [CGRP]) can contribute to the development of diarrhea, Cushing's syndrome, or facial flushing in many patients with advanced disease. Sporadic disease typically presents in the fifth or sixth decade. There may be a slight female preponderance. Familial forms of the disease tend to present at earlier ages, and the risk of concomitant or subsequent development of pheochromocytoma and hyperparathyroidism must always be considered.

Nodule Evaluation and Diagnosis

Patients with medullary carcinoma can be identified by using pathologic diagnosis or by prospective genetic screening. Separate paths are included in the guidelines algorithm depending on the method of identification used.

Sporadic MTC is usually suspected after FNA of a solitary nodule. Routine measurement of the serum calcitonin concentration is not recommended as a screen for MTC in a patient with a solitary nodule. However, reports suggest that perhaps as many as 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 prove to have MTC at thyroidectomy.[160-162] Because of the expense (the estimated cost is $12,500 per diagnosed MTC case that would not be identified by other means), routine measurement of the serum calcitonin concentration is not recommended for evaluating a patient with nodular thyroid disease.[163,164]

For patients in known kindreds with inherited MTC, prospective family screening can identify disease carriers long before clinical symptoms or signs are noted.[165] Using the traditional approach of stimulated secretion of calcitonin by either pentagastrin or calcium infusion, 65% of MEN 2A gene carriers will have abnormal calcitonin levels by age 20 years; 95% will have an increased calcitonin level by 35 years.[166] Compared with sporadic disease, the typical age of presentation for familial disease is the third decade, without sex preference. In 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.[165] 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, whereas MEN 2B and some familial MTC mutations are found within the intracellular exons 14-16 (see Table 2). 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.[167] Genetic testing for *RET* proto-oncogene mutations should be encouraged for all newly diagnosed patients with clinically apparent sporadic MTC, as well as for screening children and adults in known kindreds with inherited forms of MTC. Based on the relative frequency of mutations in certain exons, mutational analysis should start with exon 11, followed sequentially by exons 10, 16, 13, 14, and 15.[165] Although common mutations can be identified by broadly available commercial testing sources, only a limited number of sites perform the more thorough analyses that are required to identify the less common mutations. A 3% to 5% error rate is generally reported, underscoring the importance for repeat testing of at least two independently obtained blood samples in more than one laboratory to minimize the likelihood of both false-positive and false-negative results.[168]

Generally accepted approaches to preoperative workup include measurement of serum markers (calcitonin and serum carcinoembryonic antigen [CEA]) and screening patients with germline *RET* proto-oncogene mutations for pheochromocytoma (MEN 2A and 2B) and for hyperparathyroidism (MEN 2A). Before undertaking surgical therapy for MTC, it is important to diagnose and prospectively treat co-existing pheochromocytoma (using alpha-adrenergic blockade [phenoxybenzamine] with or without alpha-methyltyrosine) to avoid hypertensive crisis during surgery. Vocal cord mobility should also be evaluated (category 2B). Preoperative neck ultrasound can be considered in adults with clinical disease to evaluate for locoregional adenopathy, but the panel disagreed regarding its use in young patients identified by prospective genetic screening, in whom the frequency of nodal metastases is quite low.

Staging

Compared with differentiated thyroid carcinoma, a smaller set of staging approaches exist for MTC. 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) (these criteria are from the 6th edition of the AJCC staging manual).[60] An MTC less than 2 cm in diameter without evidence of disease outside of the thyroid gland is classified as stage I. Any larger tumor (more than 2 cm but 4 cm or less) limited to the thyroid without nodal or distant metastases is classified as stage II. The presence of level 6 nodal metastases, minimal extrathyroidal invasion, or tumor size greater than 4 cm places the patient in stage III. Tumor extending beyond the perithyroid soft tissues, involving lymph nodes beyond level 6, or spreading to distant metastatic sites is classified as stage IV.

Note that all recent follow-up studies (discussed in this manuscript) reporting on AJCC-TNM staging have referred to the 5th edition[61] and not the 6th edition.[60] 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.[169] An alternative staging classification proposed by DeGroot defines stage I disease as localized to the thyroid and stage II as limited to the thyroid or locoregional nodes.[170] Extrathyroidal or extranodal extension characterizes stage III disease, and distant metastases characterize stage IV. Using this approach, survival significantly declines with increasing stage assignment. In particular, the presence of either stage III or stage IV disease increases the risk of death from MTC at least seven-fold and carries a median disease-specific survival of 3 to 5 years.[159] A third approach, used by the National Thyroid Cancer Treatment Cooperative Study Group,[36] defines stage I disease as the premalignant lesion C-cell hyperplasia, generally only identified as an incidental finding except as a result of familial screening. Stage II disease is a primary tumor less than 1 cm without locoregional or distant metastasis. Stage III is a tumor greater than 1 cm or locoregional nodal metastasis. The presence of distant metastases defines stage IV disease.

However, these staging classifications lack other important prognostic factors. Notably absent is the age at diagnosis. Patients younger than 40 years at diagnosis have a 5- and 10-year disease-specific survival rate of about 95% and 75%, respectively, compared with 65% and 50% for those older than 40 years.[159] 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.[171,172] Despite an even younger typical age at diagnosis; however, patients with MEN 2B who have MTC are more likely than those with either MEN 2A or familial MTC to have locally aggressive disease.[172] Other factors that may be important for predicting a worse prognosis include: (1) the heterogeneity and paucity of calcitonin immunostaining of the tumor;[173] (2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level;[174] and (3) postoperative residual hypercalcitoninemia.[169] Improvement in the predictive value of the TNM staging may result from incorporation of disease type (sporadic versus familial) and the presence of bilateral versus unilateral adenopathy.[175] With more study, specific germline or somatic mutations in *RET* may also be useful predictors of disease outcome. Certainly, presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease.[176]

Surgical Management

Even with patients who have apparently sporadic disease, the possibility of MEN 2 should dictate that a *RET* proto-oncogene mutation is proven to be absent or that hyperparathyroidism and pheochromocytoma should be excluded preoperatively. Total thyroidectomy is indicated in all patients with MTC, especially because of the high frequency of bilateral disease in both sporadic and familial disease.[159] If a patient with inherited disease is diagnosed early enough, the recommendation is generally to perform total thyroidectomy by age 5 years, especially in patients with codon 609, 611, 618, 620, 630, or 634 *RET* (risk level II) mutations.[177] Total thyroidectomy is recommended in the first year of life or at diagnosis for MEN 2B patients or carriers of codon 883, 918, or 922 *RET* (risk level III) mutations. However, for patients with codon 768, 790, 791, 891, and 804 *RET* (risk level I) mutations, the lethality of MTC may be lower than with other *RET* mutations. In patients with these *RET* mutations, annual provocative (calcium) calcitonin testing may be continued; total thyroidectomy and central node dissection may be deferred until tests become abnormal after the age of 5 years.[178] Delaying thyroidectomy until age 10 years may also be appropriate for children with risk level I mutations because of the late onset of MTC development.[179] A recent 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.[180]

Patients with pheochromocytomas must be treated preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery on the thyroid. Forced hydration along with alpha blockade is 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.

Variations in surgical strategy depend on the risk for locoregional node metastases and incorporation of simultaneous parathyroid resection for hyperparathyroidism. A bilateral central neck dissection (level VI) is preferred for all patients with pathologically demonstrated MTC and for those with MEN 2B. For those patients with MEN 2A who undergo prophylactic thyroidectomy, bilateral central neck dissection (level VI) should be considered if patients have an increased calcium-stimulated calcitonin test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II to 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. With a concurrent diagnosis of hyperparathyroidism in MEN 2A, 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. Postoperative thyroid hormone therapy is indicated; however, TSH suppression is not appropriate, because C cells lack TSH receptors.

Adjuvant Radiation Therapy

External-beam RT has not been adequately studied as adjuvant therapy in medullary carcinoma. Slight improvements have been reported in local disease-free survival after external-beam RT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement. However, most centers do not have extensive experience with adjuvant RT for this disease. When external-beam RT 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 five fractions to the thyroid bed.[118] Adjuvant RT can be considered for patients with T4a disease. As for differentiated carcinoma, external-beam RT can also be given to palliate painful or progressing bone metastases.

Persistently Increased Calcitonin

Serum concentrations of calcitonin and CEA should be measured 2 or 3 months postoperatively. Those patients whose calcitonin level is positive should receive additional imaging. Neck ultrasound can be considered in patients with negative imaging who are asymptomatic. 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 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 staging imaging is therefore not unreasonable 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.[181] 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.[169,182] Routine lymphadenectomy or excision of palpable tumor generally fails to normalize the serum calcitonin concentrations in such patients; therefore, some have focused attention 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 stimulated serum calcitonin levels in 4 of 11 patients at least 2 years postoperatively.[183] 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.[184,185]

When repeat surgery is planned for curative intent, preoperative assessment should include locoregional imaging (such as ultrasonography of the neck and upper mediastinum) and attempts to exclude patients with distant metastases, which may include CT of the chest, and CT or MRI of the abdomen. Laparoscopic assessment of the liver may be performed if distant metastases are not detected by this diagnostic approach.[185] However, in the absence of long-term outcomes, application of this approach should probably be limited to those centers with experience with these patients. Other imaging procedures occasionally used include bone scintigraphy; ^{111}In-pentetreotide, 6-^{18}F-flourodopamine, and ^{18}F-FDG positron emission tomography; ^{99m}Tc pentavalent dimercaptosuccinic acid, ^{99m}Tc-sestamibi, or tetrofosmin; and systemic venous sampling by catheterization of the hepatic veins, both internal jugular veins, and the innominate veins, with measurements of serum calcitonin before and after stimulation. Only patients with overt disease in the neck and no distant metastases should undergo re-operative neck surgery.

Postoperative Management and Surveillance

Measurements of serum calcitonin and CEA levels are the cornerstone of postoperative assessment for residual disease. For patients with a negative calcitonin level, neck ultrasound could be considered. Patients with undetectable calcitonin levels can subsequently be followed with annual measurements of serum markers and additional studies or more frequent testing as indicated. Nonetheless, the likelihood of significant residual disease is very low in patients with a negative basal calcitonin level in a sensitive assay. If the patient has MEN 2B or 2A, annual screening for pheochromocytoma and hyperparathyroidism should also be performed. For some *RET* mutations (eg, codons 768, 790, V804M, or 891), less frequent screening may be appropriate. Patients with abnormal serum markers should be considered for additional diagnostic imaging to identify the location of tumor. The panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but there is insufficient evidence to recommend any particular choice or combination of tests.

For the asymptomatic patient with abnormal markers in whom imaging fails to identify foci of disease, the panel recommends conservative annual surveillance with repeat measurement of the serum markers. Neck ultrasound scanning may be considered to examine the superior mediastinum, the bilateral central compartment, and the bilateral lateral neck compartments. For asymptomatic patients with abnormal markers and repeated negative imaging, continued observation or consideration of cervical re-operation is recommended if incomplete primary surgery was performed. 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

When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended; if disease is unresectable, then RT is recommended. In the presence of distant metastases, locoregional disease may still be considered for removal or RT in selected instances. Similarly, distant metastases that are causing symptoms (such as those in bone) could be considered for resection, RT, radiofrequency ablation, chemoembolization, or other regional treatment. These interventions may be considered for asymptomatic distant metastases but observation is acceptable, given the lack of data regarding alteration in outcome. In the setting of disseminated distant symptomatic metastases, the guidelines recommend the following: (1) external-beam RT can be administered in the setting of focal symptoms; (2) systemic chemotherapy can be administered, using dacarbazine or combinations including dacarbazine;[81,186] (3) when available, a clinical trial; or (4) bisphosphonate therapy can be considered for bone metastases. Currently, phase II trials are ongoing, studying the effectiveness of novel multi-targeted therapies including AMG-706, Zactima (ZD6474; in inherited disease only), and sorafenib (BAY 43-9006). A recent study in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with ^{131}I;[187] overall survival was improved in the subset of patients with calcitonin doubling times less than 2 years.

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%. Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 65 years. Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[35] Approximately 50% of patients with anaplastic 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.[188] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain.

Patients with anaplastic carcinoma present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[189] The lungs and pleura are the most common site of distant metastases, being present in up to 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 carcinomas are considered stage IV (A, B, or C) (see Table 1). The T4 category includes: (1) T4a tumors which are intrathyroidal and surgically resectable; (2) T4b tumors which are extrathyroidal and not surgically resectable.

The diagnosis of anaplastic carcinoma is usually established by FNA or surgical biopsy. Diagnostic procedures include a complete blood count, serum calcium, and TSH level. CT scans of the neck and mediastinum can accurately determine the extent of the thyroid tumor and can identify tumor invasion of the great vessels and upper aero-digestive tract structures.[190] Most pulmonary metastases are nodules that can be detected by routine chest radiographs. Bone lesions are usually lytic.

Treatment and Prognosis

No effective therapy exists for anaplastic carcinoma, and the disease is uniformly fatal. The median survival from diagnosis ranges from 3 to 7 months. The 1- and 5-year survival rates are about 25% and 5%, respectively.[189] Death is attributable to upper airway obstruction and suffocation (often despite tracheostomy) in 50% of these patients, and to a combination of complications of local and distant disease and/or therapy in the remaining patients. 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.[191] Other variables that may predict a worse prognosis include older age at diagnosis, male sex, and dyspnea as a presenting symptom.

Except for patients whose tumors are small and confined entirely to the thyroid or readily excised structures, total thyroidectomy with complete tumor resection has not been shown to prolong survival.[191,192] External-beam RT, administered in conventional doses, also does not prolong survival. Although up to 40% of patients may respond initially to RT, most have local recurrence. Treatment with single-drug chemotherapy also does not improve survival or control of disease in the neck, although perhaps 20% of patients have some response in distant metastases. The introduction of hyperfractionated RT, 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.[193] Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin, followed by debulking surgery in responsive patients. However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival. Paclitaxel has been tested in newly diagnosed patients and may provide some palliative benefit.[194]

A patient with anaplastic thyroid cancer had a durable complete response in a phase I trial of the agent combretastatin A4 phosphate (CA4P), and he has been disease free for more than 3 years.[195] CA4P is now being examined in phase II studies both as (1) single-agent treatment for patients with metastatic or unresponsive anaplastic carcinoma, and (2) in combination with doxorubicin, cisplatin, and radiotherapy for newly diagnosed patients with locally advanced disease. A vascular targeting agent, CA4P causes a rapid and selective shutdown of tumor blood vessels leading to massive necrosis. CA4P may be efficacious when combined with conventional chemotherapeutic drugs or radiation.[196] However, CA4P is associated with some cardiovascular toxicity; thus, patients will have to be carefully selected.[197]

Once the diagnosis of anaplastic carcinoma is identified pathologically, the panel recognizes the importance of rapidly determining the potential for local resection, because 50% of all patients die of uncontrollable disease in the neck. Patients should undergo a neck CT scan and a chest x-ray. If the disease is deemed likely to be resectable, an attempt at total or near-total thyroidectomy should be made, with selective resection of all involved local or regional structures and nodes. The guidelines also recommend that patients with tumors that cannot be completely removed should, instead, receive efforts to protect their airway, including the possibility of a prophylactic tracheostomy. All patients, regardless of surgical resection, should then undergo multimodality therapy. Although optimal results have been reported with hyperfractionated RT combined with chemotherapy, the panel acknowledged that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported. The guidelines do not recommend particular chemotherapeutic agents, either for radiosensitization or full-dose therapy, because of a lack of clear evidence of efficacy for any particular regimen. Considering alternative approaches to RT and chemotherapy, particularly in clinical trials, is therefore recommended.

Disclosures for the NCCN Thyroid Carcinoma Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Abbott; Amgen, Inc; AstraZeneca; Bristol-Myers Squibb; and Genzyme Corp. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

Figure 1:

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

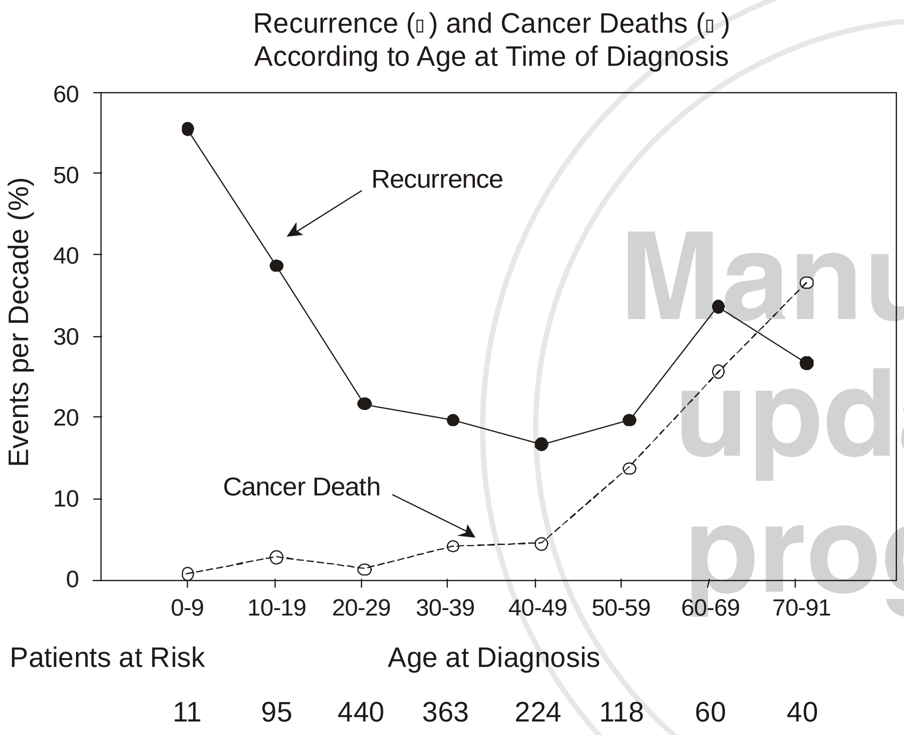

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Figure 2:

Relationship of cancer recurrence and mortality to tumor size

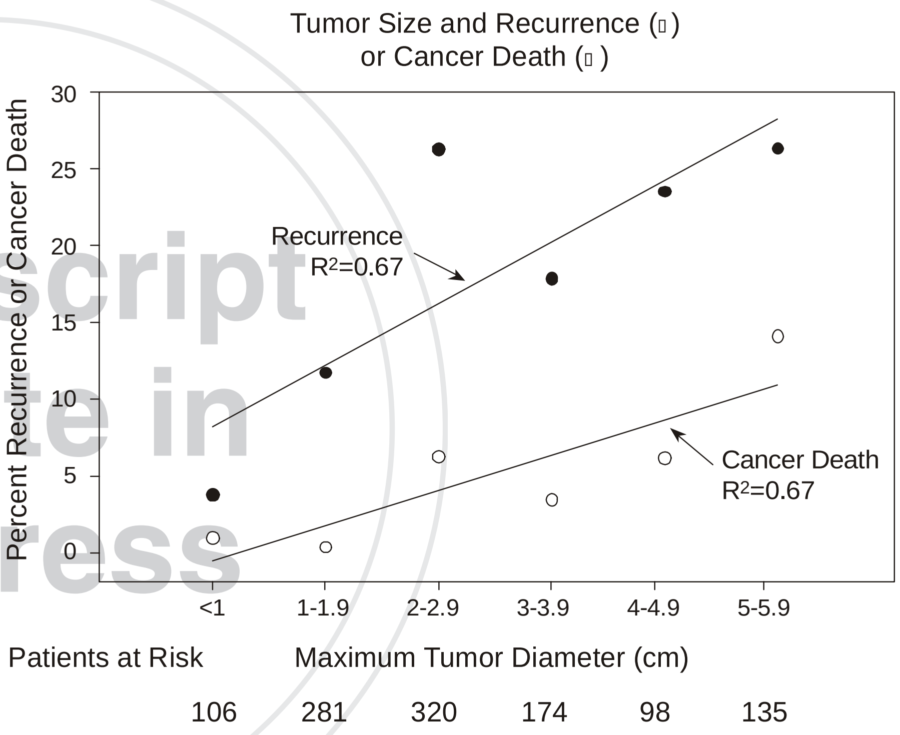

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Table 2

Mutations of the RET Proto-oncogene Associated with MEN 2 and Familial Medullary Thyroid Cancer (FMTC)

Affected Codon/Exon	Clinical Syndrome(s)	Percentage of All MEN 2 Mutations
609/10	MEN 2A, FMTC	0 - 1%
611/10	MEN 2A, FMTC	2 - 3%
618/10	MEN 2A, FMTC	3 - 5%
620/10	MEN 2A, FMTC	6 - 8%
630/11	MEN 2A, FMTC	0 - 1%
634/11	MEN 2A	80-90%
635/11	MEN 2A	Rare
637/11	MEN 2A	Rare
768/13	FMTC	Rare
790/13	MEN 2A, FMTC	Rare
791/13	FMTC	Rare
804/13	MEN 2A, FMTC	0 - 1%
883/15	MEN 2B	Rare
891/15	FMTC	Rare
918/16	MEN 2B	3 - 5%
922/16	MEN 2B	Rare

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