Overview

Epidemiology

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of approximately 5% in the United States population aged 50 years and older.1–3 Nodules are even more prevalent when the thyroid gland is examined at autopsy or surgery, or when using ultrasound, and 50% of these have nodules, which are almost always benign.2,4 New nodules develop at a rate of approximately 0.1% per year beginning in early life, but at a much higher rate (~2% per year) after exposure to head and neck irradiation.5,6

By contrast, thyroid carcinoma is uncommon. For the United States population, the lifetime risk of
Thyroid carcinoma is a type of cancer that affects the thyroid gland, which is located in the front of the neck. It is more common in women than in men and is diagnosed in the United States annually. The disease has three main histologic types: differentiated (including papillary, follicular, and Hürthle cell), medullary, and anaplastic (aggressive undifferentiated tumor). Of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, 80% had papillary carcinoma, 11% had follicular carcinoma, 3% had Hürthle cell carcinoma, 4% had medullary carcinoma, and 2% had anaplastic thyroid carcinoma. The 10-year relative survival rates for patients with papillary, follicular, and Hürthle cell carcinomas were 93%, 85%, and 76%, respectively. This discussion focuses on papillary, follicular, Hürthle cell, and anaplastic thyroid carcinoma. Medullary thyroid carcinoma was previously published in this journal (May 2010). A complete discussion of thyroid carcinoma, including medullary thyroid carcinoma, is available.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Thyroid Carcinoma 1:2010

CLINICAL PRESENTATION

• Solitary nodule > 1-1.5 cm in diameter
• Increased suspicion if any of the following are present:
  ▶ Age < 15 y
  ▶ Male sex
  ▶ Nodule > 4 cm in diameter
  ▶ History of radiation exposure
  ▶ History of diseases associated with thyroid cancer:
    ◆ Pheochromocytoma
    ◆ MEN2
    ◆ Familial adenomatous polyposis
    ◆ Carney complex
    ◆ Cowden’s syndrome
  ▶ Suspicious criteria by ultrasound
  ▶ Incidentally identified focal PET positive lesion in the thyroid

WORKUP

Clinically euthyroid:
• TSH measurement
• Ultrasound of thyroid and central neck
• Ultrasound of the lateral neck (category 2B)
• FNA of nodule
• FNA of clinically suspicious lymph nodes

Thyroid nodule with unknown TSH

Nodules < 1 cm in diameter without suspicious findings and without suspicious lymph nodes by ultrasound, or simple cyst

• Follow-up as clinically indicated
• Consider lateral neck ultrasound
• If findings consistent with criteria of increased suspicion - see pathway above

Thyroid nodule with low TSH

Radiiodine imaging

Cold

• Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)

Hot

FNA

See FNA Results (facing page)

Papillary carcinoma, finding postlobectomy for benign disease

See Primary Treatment (page 1234)

NODULE EVALUATION

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

Patients with elevated thyroid stimulating hormone (TSH) levels may have an increased risk of malignancy.

Consider surgery after fine-needle aspiration (FNA).
**Thyroid Carcinoma 1:2010**

### NODULE EVALUATION

#### FNA RESULTS

- **Carcinoma**
  - Papillary or suspicious for papillary
    - See Primary Treatment (page 1233)
  - Medullary or suspicious for medullary
    - See Primary Treatment (available online, in these guidelines, at www.NCCN.org [MEDU-1])
  - Anaplastic or suspicious for anaplastic
    - See Primary Treatment (page 1249)

- **Follicular or Hürthle cell neoplasm**
  - TSH high or normal
    - Surgery
  - TSH low
    - Radiiodine imaging
      - Hot
      - Cold
        - Surgery
        - Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)

- **Follicular lesion of undetermined significance**
  - TSH high or normal
  - TSH low
    - Radiiodine imaging
      - Hot
      - Cold
        - Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)

- **Thyroid lymphoma**
  - See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Hodgkin's Lymphoma

- **Insufficient biopsy, nondiagnostic**
  - Cystic
    - Correlate with ultrasound, reaspirate suspicious areas
  - Solid
    - Repeat FNA, consider ultrasound guidance and immediate cytologic review or consider surgery

- **Benign**
  - Observe
  - If nodule growth, repeat FNA or consider surgery

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org*

Diagnostic categories for FNA results reflect NCI State-of-the-Science Conference, available at [http://www.cytojournal.com/content/5/1/6](http://www.cytojournal.com/content/5/1/6). Cytology reports should be interpreted in light of terminology used by local cytopathologists.

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**Footnotes**

- Alternative term: suspicious for follicular or Hürthle cell neoplasm. Estimated risk of malignancy is 20%-30%.
- Alternative terms include: atypia of undetermined significance, rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%-10%.
- Includes nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, and Hashimoto's thyroiditis. Estimated risk of malignancy is < 1%.
- Surgery usually means a diagnostic lobectomy for these follicular lesions. Consider total thyroidectomy for bilateral disease, unilateral disease > 4 cm (especially in men), or patient preference.

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PRINCIPLES OF TSH SUPPRESSION

Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hurthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH. In general, patients with known residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range. Patients who remain disease-free for several years can probably have their TSH levels maintained within the reference range. Given the potential toxicities associated with TSH-suppressive doses of levothyroxine—including cardiac tachyarrhythmias (especially in the elderly), bone demineralization (particularly in postmenopausal women), and frank symptoms of thyrotoxicosis—the risks and benefits of TSH-suppressive therapy must be balanced for each individual patient. Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d).
PRINCIPLES OF TSH SUPPRESSION

Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hurthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH. In general, patients with known residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range. Patients who remain disease-free for several years can probably have their TSH levels maintained within the reference range. Given the potential toxicities associated with TSH-suppressive doses of levothyroxine—including cardiac tachyarrhythmias (especially in the elderly), bone demineralization (particularly in postmenopausal women), and frank symptoms of thyrotoxicosis—the risks and benefits of TSH-suppressive therapy must be balanced for each individual patient. Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d).

**Papillary carcinoma FNA positive**
- Consider chest x-ray
- Thyroid ultrasound, including lateral neck, if not previously done
- CT/MRI for fixed, bulky, or substernal lesions (avoid iodinated contrast, unless essential)
- Evaluate vocal cord mobility

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

**Total thyroidectomy**
- If lymph node(s) palpable or biopsy positive:
  - Central neck dissection (level VI)
  - Lateral neck dissection (levels II-IV, consider level V, sparing spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle); consider preservation of the cervical sensory nerves
- If node(s) negative, consider prophylactic central neck dissection (level VI; category 2B)

**Papillary carcinoma FNA positive**
- Consider chest x-ray
- Thyroid ultrasound, including lateral neck, if not previously done
- CT/MRI for fixed, bulky, or substernal lesions (avoid iodinated contrast, unless essential)
- Evaluate vocal cord mobility

**Indications for total thyroidectomy or lobectomy:**
- Age 15–45 y
- No prior radiation
- No distant metastases
- No cervical lymph node metastases
- No extrathyroidal extension
- Tumor < 4 cm in diameter
- No aggressive variant

**Total thyroidectomy (most common; category 2B)**
- Aggressive variant
- Macroscopic multifocal disease
- Positive isthmus margins
- Cervical lymph node metastases
- Gross extrathyroidal extension

**Lobectomy + isthmusectomy (category 2B)**
- Negative margins
- No contralateral lesion

See Postsurgical Evaluation (page 1235)

Completion of thyroidectomy
- Consider thyroglobulin measurement
- Consider levothyroxine therapy to keep TSH low or normal

See Surveillance and Maintenance (page 1237)

There is a potential role for frozen section if FNA is suspicious but not diagnostic for papillary carcinoma.

For microcarcinoma, a total thyroidectomy may not be needed. Age is an approximation and not an absolute determination (i.e., > 45 y is not an absolute indication).

Tall cell variant, columnar cell, or poorly differentiated features.

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

See Principles of TSH Suppression (opposite page).
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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PAPILLARY CARCINOMA

POSTSURGICAL EVALUATION AFTER THYROIDECTOMY

No gross residual disease in neck

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

Resectable

Resect, if possible

Gross residual disease

Consider radioiodine (RAI) therapy based on clinical indications for RAI³

No gross residual disease

TSH + thyroglobulin measurement + antithyroglobulin antibodies (2-12 wk postoperatively)

Not considering RAI therapy because of lack of clinical indication for RAI³

Unresectable

Inadequate uptake

RT

Adequate uptake

- Radiiodine treatment
- Post-treatment ¹³¹I imaging
- RT

No imaging performed

Supress TSH with levothyroxine⁶

³See Principles of TSH Suppression (page 1232).
⁴Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.
⁵See Postsurgical Therapy (page 1236)
⁶See Surveillance and Maintenance (page 1237)
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POSTSURGICAL THERAPY

2-12 wk post-thyroidectomy: no gross residual disease in neck

- Total body radioiodine imaging (category 2B) with adequate TSH stimulation (thyroid withdrawal or recombinant human TSH [rTSH] stimulation) or Clinical indication for radioiodine therapy
  - Suspected or proven thyroid bed uptake

- Thyroglobulin < 1 ng/mL with negative antithyroglobulin antibodies and radioiodine imaging negative
  - No radioiodine treatment

- T4 (surgically evident gross extrathyroidal extension) and age > 45 y
  - Consider RT

- Adjuvant radioiodine ablation (30-100 mCi) to destroy residual thyroid function; posttreatment imaging

- All others
  - Suppress TSH with levothyroxine

- Radioiodine treatment (100-200 mCi) and posttreatment imaging or consider dosimetry for distant metastasis

- Suspected or proven radioiodine responsive residual tumor

- See Surveillance and Maintenance (facing page)

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*See Principles of TSH Suppression (page 1232).

*Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

*All patients should be examined, and palpable neck disease should be surgically resected before radioiodine treatment.

*The administered activity of RAI therapy should be adjusted for pediatric patients.
**Thyroid Carcinoma 1:2010**

### 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 in patients previously treated with RAI and with negative TSH-suppressed thyroglobulin and antithyroglobulin antibodies
- Consider TSH-stimulated radioiodine imaging in patients with T3-4 or M1 at initial staging, or with abnormal thyroglobulin levels (either TSH-suppressed or TSH-stimulated), abnormal antithyroglobulin antibodies, or abnormal ultrasound during surveillance
- If detectable thyroglobulin, distant metastases, or soft tissue invasion on initial staging, radioiodine imaging every 12 mo until no response is seen to RAI treatment in iodine responsive tumors (either withdrawal of thyroid hormone or rhTSH)
- If $^{131}$I imaging negative and stimulated Tg > 2-5 ng/mL, consider additional nonradioiodine imaging (e.g., FDG-PET ± CT if Tg ≥ 10 ng/mL)

### RECURRENT DISEASE

- Stimulated Tg 1-10 ng/mL
  - Nonresectable tumors
  - Nonradioiodine responsive
  - Suppress TSH with levothyroxine

- Stimulated Tg > 10 ng/mL
  - Scans (including PET) negative
  - Consider radioiodine therapy with 100-150 mCi, posttreatment I imaging (category 3)

- Metastatic disease
  - See Treatment of Metastases (page 1238)

### Locoregional recurrence

- Surgery (preferred) if resectable and/or Radioidine treatment, if radioiodine imaging positive and/or RT, if radioiodine imaging negative

### METASTATIC DISEASE

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

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*See Principles of TSH Suppression (page 1232).*

*Subgroup of low-risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.*

*In selected patients who may be at higher risk for residual/recurrent disease (e.g., patients with N1 disease), obtain a stimulated thyroglobulin and consider concomitant diagnostic RAI imaging. With a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (i.e., RAI is often beneficial in iodine-avid disease but not in non–iodine-avid disease).*

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

*Consider preoperative vocal cord assessment, if central neck recurrence.*
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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### FOLLICULAR CARCINOMA

**PATHOLOGY FINDING**

- Follicular neoplasm or
- Follicular lesion of undetermined significance (see page 1231)

**DIAGNOSTIC PROCEDURES**

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

**PRIMARY TREATMENT**

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

#### Benign

- Levothyroxine therapy to keep TSH normal\(^b\)

#### Follicular carcinoma

- Invasive cancer (extensive vascular invasion)

- Completion of thyroidectomy

#### Minimally invasive cancer\(^a\)

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

- Observe

- See Postsurgical Evaluation (page 1240)

#### Lobectomy/isthmusectomy

- Completion of thyroidectomy

- Or

- Consider levothyroxine therapy to keep TSH normal\(^b\)

- See Surveillance and Maintenance (page 1242)

- Observe

**Notes**

- \(^a\)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.

- \(^b\)See Principles of TSH Suppression (page 1232).
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

See Principles of TSH Suppression (page 1232).

Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.
POSTSURGICAL EVALUATION AFTER THYROIDECTOMY

See Postsurgical Therapy (facing page)

TSH + thyroglobulin measurement + antithyroglobulin antibodies (2-12 wk postoperatively)

No gross residual disease in neck

Gross residual disease in neck

Unresectable

Resect, if possible

No gross residual disease

Gross residual disease

Inadequate uptake

No imaging performed

RT

Radioiodine treatment

Total body radioiodine imaging (category 2B)

Suspected or proven radioiodine responsive residual tumor

Suppress TSH with levothyroxine

See Surveillance and Maintenance (page 1242)

Adjuvant radioiodine ablation (30-100 mCi) to destroy residual thyroid function and posttreatment imaging

Radioiodine treatment (100-200 mCi) and posttreatment imaging or consider dosimetry for distant metastasis

See Principles of TSH Suppression (page 1232).

Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

All patients should be examined, and palpable neck disease should be surgically resected before radioiodine treatment.

The administered activity of RAI therapy should be adjusted for pediatric patients.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
**TREATMENT OF METASTASES**

- **Metastatic disease**
  - Continue to suppress TSH with levothyroxine\(^b\)

- **Bone**
  - Consider neurosurgical resection\(^j\)
  - Radioiodine treatment with rhTSH and steroid prophylaxis, if radioiodine imaging positive with consideration of dosimetry to maximize dosing and/or
  - Image-guided RT\(^j\)

- **Sites other than CNS**
  - Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities and/or
  - Radioiodine treatment, if radioiodine imaging positive with consideration of dosimetry to maximize dosing and/or
  - RT
  - Consider bisphosphonate therapy
  - Consider embolization of metastases

- Consider surgical resection and/or RT of selected, enlarging, or symptomatic metastases and/or
  - Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing and/or
  - For clinically progressive or symptomatic disease: clinical trials for nonradioiodine responsive tumors\(^k\); consider small molecule kinase inhibitor\(^l\) or systemic therapy (if trial not available) or
  - Best supportive care

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\(^b\) See Principles of TSH Suppression (page 1232).
\(^j\) For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred.
\(^k\) Cytotoxic chemotherapy has been shown to have minimal efficacy. Clinical trials investigating novel targeted therapies are ongoing. See clinical trials available at the NCCN member institutions (www.NCCN.org).
\(^l\) Although not FDA-approved for treatment of thyroid cancer commercially available small-molecule kinase inhibitors (such as sorafenib or sunitinib) can be considered if clinical trials are not available or appropriate.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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HÜRTHLE CELL CARCINOMA

POSTSURGICAL EVALUATION
AFTER THYROIDECTOMY

No gross residual disease in neck

Resectable → Resect, if possible

Gross residual disease

Unresectable

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

Inadequate uptake → RT

Adequate uptake

• Radioidine treatment
• Posttreatment \(^{131}\)I imaging
• RT

No scan performed

Consider radioiodine (RAI) therapy based on clinical indications for RAI\(^e\)

See Postsurgical Therapy (page 1246)

Suppress TSH with levothyroxine\(^d\)

See Surveillance and Maintenance (page 1247)

No gross residual disease

TSH + thyroglobulin measurement + antithyroglobulin antibodies (2-12 wk postoperatively)

Not considering RAI therapy because of lack of clinical indication for RAI\(^e\)

See Surveillance and Maintenance (page 1247)

Gross residual disease in neck

Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

\(^d\) See Principles of TSH Suppression (page 1232).
\(^e\) Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

\(^a\) Possible benefit to reduce recurrence must be balanced with risk of hypoparathyroidism.
\(^b\) Also known as oxyphilic.
\(^c\) Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.

\(^e\) Not considering RAI therapy because of lack of clinical indication for RAI.
POSTSURGICAL THERAPY

Thyroglobulin < 1 ng/mL with negative antithyroglobulin antibodies and radiiodine imaging negative → No radioiodine treatment

Total body radiiodine imaging (category 2B) with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) or Clinical indication for RAI therapy\(^{\#}\) (category 2B)

Suspected\(^{\#}\) or proven thyroid bed uptake → Adjuvant radiiodine ablation (30-100 mCi)\(^{\circ}\) to destroy residual thyroid function and posttreatment imaging

Adjuvant radioiodine ablation (30-100 mCi)\(^{\circ}\) to destroy residual thyroid function and posttreatment imaging

Radioiodine treatment (100-200 mCi)\(^{\circ}\) and posttreatment imaging or consider dosimetry for distant metastasis

T4 (surgically evident gross extrathyroidal extension) and age > 45 y → Consider RT

All others → Suppress TSH with levothyroxine\(^{d}\)

See Surveillance and Maintenance (facing page)

\(^{d}\)See Principles of TSH Suppression (page 1232).

\(^{\#}\)Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

\(^{\circ}\)All patients should be examined and palpable neck disease should be surgically resected before radioiodine treatment.

\(^{\circ}\)The administered activity of RAI therapy should be adjusted for pediatric patients.
### Thyroid Carcinoma 1:2010

**HÜRTHLE CELL CARCINOMA**

#### 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 in patients previously treated with RAI and with negative TSH-suppressed thyroglobulin and antithyroglobulin antibodies
- Consider TSH-stimulated radionuclide imaging in patients with T3-4 or M1 at initial staging, or with abnormal thyroglobulin levels (either TSH-suppressed or TSH-stimulated), abnormal antithyroglobulin antibodies, or abnormal ultrasound during surveillance
- If detectable thyroglobulin, distant metastases, or soft tissue invasion on initial staging, radionuclide imaging every 12 mo until no response is seen to RAI treatment in iodine responsive tumors (either withdrawal of thyroid hormone or rhTSH)
- If $^{131}I$ imaging negative and stimulated Tg $>2-5$ ng/mL, consider additional nonradioiodine imaging (e.g., FDG-PET ± CT if Tg $>10$ ng/mL)

#### RECURRENT DISEASE

- Stimulated Tg 1-10 ng/mL
- Nonresectable tumors
- Nonradioiodine responsive
  - Suppress TSH with levothyroxine

- Locoregional recurrence
  - Surgery (preferred) if resectable and/or
  - Radionuclide treatment, if radionuclide imaging positive and/or
  - RT, if radionuclide imaging negative

- Stimulated Tg $>10$ ng/mL
- Scans (including PET) negative
  - Consider radioiodine therapy with 100-150 mCi, posttreatment $^{131}I$ imaging (category 2B)

- Metastatic disease
  - See Treatment of Metastases (page 1248)

**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 in patients previously treated with RAI and with negative TSH-suppressed thyroglobulin and antithyroglobulin antibodies |
| Consider TSH-stimulated radionuclide imaging in patients with T3-4 or M1 at initial staging, or with abnormal thyroglobulin levels (either TSH-suppressed or TSH-stimulated), abnormal antithyroglobulin antibodies, or abnormal ultrasound during surveillance |
| If detectable thyroglobulin, distant metastases, or soft tissue invasion on initial staging, radionuclide imaging every 12 mo until no response is seen to RAI treatment in iodine responsive tumors (either withdrawal of thyroid hormone or rhTSH) |
| If $^{131}I$ imaging negative and stimulated Tg $>2-5$ ng/mL, consider additional nonradioiodine imaging (e.g., FDG-PET ± CT if Tg $>10$ ng/mL) |

**RECURRENT DISEASE**

- Stimulated Tg 1-10 ng/mL
  - Nonresectable tumors
  - Nonradioiodine responsive
    - Suppress TSH with levothyroxine

- Locoregional recurrence
  - Surgery (preferred) if resectable and/or
  - Radionuclide treatment, if radionuclide imaging positive and/or
  - RT, if radionuclide imaging negative

- Stimulated Tg $>10$ ng/mL
  - Scans (including PET) negative
    - Consider radioiodine therapy with 100-150 mCi, posttreatment $^{131}I$ imaging (category 2B)

- Metastatic disease
  - See Treatment of Metastases (page 1248)

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**See Principles of TSH Suppression (page 1232).**

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

**In selected patients who may be at higher risk for residual/recurrent disease (e.g., patients with N1 disease), obtain a stimulated thyroglobulin and consider concomitant diagnostic RAI imaging. With a positive stimulated Tg, the concomitant RAI imaging may help determine whether treatment with RAI is indicated (i.e., RAI is often beneficial in iodine-avid disease but not in non-iodine–avid disease).**

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

**Consider preoperative vocal cord assessment, if central neck recurrence.**

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TREATMENT OF METASTASES

Metastatic disease
- Continue to suppress TSH with levothyroxine

CNS
- Consider neurosurgical resection and/or Image-guided RT

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

Sites other than CNS
- Consider surgical resection and/or RT of selected, enlarging, or symptomatic metastases and/or
- Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing and/or
- For clinically progressive or symptomatic disease: clinical trials for nonradioiodine responsive tumors; consider small molecule kinase inhibitor or systemic therapy (if trial not available) or
- Best supportive care

See Principles of TSH Suppression (page 1232).

For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred.

Cytotoxic chemotherapy has been show to have minimal efficacy. Clinical trials investigating novel targeted therapies are ongoing. See clinicals trials available at the NCCN Member Institutions (www.NCCN.org).

Although not FDA-approved for treatment of thyroid cancer, commercially available small-molecule kinase inhibitors (such as sorafenib of sunitinib can be considered if clinical trials are not available or appropriate.
TREATMENT OF METASTASES

CNS

Bone

Sites other than CNS

Metastatic disease

Continue to suppress TSH with levothyroxine

Consider neurosurgical resection and/or Image-guided RT

...some text...

Consider surgical resection, if symptomatic or asymptomatic in weight-bearing extremities and/or RT

Consider embolization of metastases

Consider surgical resection and/or RT of selected, enlarging, or symptomatic metastases and/or Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing and/or For clinically progressive or symptomatic disease: clinical trials for nonradioiodine responsive tumors consider small molecule kinase inhibitor or systemic therapy (if trial not available) or Best supportive care

...some text...

ANAPLASTIC CARCINOMA

FNA OR CORE BIOPSY FINDING

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT

Anaplastic carcinoma\(^a\)

\(^{a}\)An FNA diagnosis suspicious for anaplastic carcinoma should consider core biopsy.
online on the NCCN web site (www.NCCN.org).

In 2009, approximately 1630 cancer deaths occurred among persons living with thyroid carcinoma in the United States.8 Anaplastic thyroid carcinoma is almost uniformly lethal; however, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases. Although thyroid carcinoma occurs more often in women, mortality rates are higher for men, probably because men are usually older at diagnosis.7,13

The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004, but mortality rates decreased more than 44%.7 From 1975 to 2004, thyroid cancer rates in the United States doubled.14 Because overall mortality has remained stable since 1975, the increasing incidence probably partially reflects earlier detection of subclinical disease (i.e., small papillary cancers), although even microcarcinomas can metastasize regionally, thereby increasing eventual recurrence risk.14,15 However, recent data show the incidence has increased across all tumor sizes.16,17 The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.8

The Challenge of Managing Differentiated Thyroid Carcinoma
Managing differentiated (i.e., papillary, follicular, and Hürthle cell) thyroid carcinoma can be a challenge, because no prospective randomized trials of treatment have been performed. 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.16 The preferred treatment is surgery, whenever possible, followed by radioiodine (131I) and thyroxine therapy in many patients. External-beam 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 carcinogetic action of ionizing radiation. A child’s thyroid gland has one of the highest risks for developing cancer of any organ. In fact, the thyroid gland is the only organ linked to risk at approximately 0.10 Gy by convincing evidence.5 The risk for radiation-induced thyroid carcinoma is greater in women, certain Jewish populations, and patients with a family history of thyroid carcinoma,19 suggesting that genetic factors are also important in its development. Beginning within 5 years of irradiation, new nodules develop at a rate of approximately 2% annually, reaching a peak incidence within 30 years of irradiation but remaining high at 40 years.5,6

In adults, the risk of developing thyroid carcinoma after exposure to 131I seems to be small or nonexistent.20 After the Chernobyl nuclear reactor accident in 1986, many children developed papillary thyroid carcinoma after exposure to radioiodine fallout. It became evident that 131I and other short-lived radioiodines were potent thyroid carcinogens in children, particularly those younger than 10 years at exposure.21 Although radiation-induced papillary thyroid cancer usually appears more aggressive histologically and has high recurrence rates, the prognosis for survival is not clearly different from that of spontaneously occurring tumors.22,23 Iodine deficiency is associated with follicular and anaplastic thyroid carcinoma.

Differentiated Thyroid Carcinoma
Clinical Presentation and Diagnosis
Differentiated (i.e., papillary, follicular, or Hürthle cell) thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. However, evaluating all nodules for malignancy is difficult, because benign nodules are so prevalent and because thyroid carcinoma is so uncommon.1,24,25 Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their diagnosis. Approximately 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 noticed first by the patient, usually as asymptomatic nodules.1,24 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.\textsuperscript{11}

**Factors Affecting Risk for Malignancy**

Nodule size affects the risk for malignancy and the clinical evaluation. Thyroid nodules smaller than 1 cm occur with such frequency in the asymptomatic general population that they are often found serendipitously during imaging studies for other head or neck problems. Often termed incidentalomas, nodules smaller than 1 cm are typically clinically benign lesions and usually do not require biopsy, unless there are suspicious findings (see page 1231).\textsuperscript{4,20,27} In select cases, following up these nodules with serial ultrasounds may be reasonable. By contrast, nodules larger than 4 cm in diameter pose a somewhat higher risk for malignancy. Fine-needle aspiration (FNA) is the preferred procedure for evaluating suspicious thyroid nodules.\textsuperscript{3,25}

The Society of Radiologists in Ultrasound wrote a consensus statement about managing thyroid nodules identified at thyroid ultrasonography. Their recommendations describe which nodules should undergo FNA based on nodule size and ultrasound characteristics, and on clinical features that might predict risk for morbidity from an undiagnosed malignancy.\textsuperscript{28} Suspicious criteria found using ultrasound include central hypervascularity, microcalcifications, and irregular borders.

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present (see page 1230).\textsuperscript{29} For example, the likelihood that a nodule is malignant increases approximately 7-fold if it is very firm, is fixed to adjacent structures, is growing rapidly, is associated with enlarged regional lymph nodes, or causes vocal cord paralysis, or if symptoms of invasion into neck structures are present.\textsuperscript{29,30} Family history of thyroid cancer is also indicative of malignancy. If 2 or more of these features are present, the likelihood of thyroid cancer is virtually assured; however, this is a rare situation.\textsuperscript{30}

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 in men. Other factors that increase the suspicion of malignancy include 1) a history of head and neck irradiation; 2) a family history of diseases associated with thyroid carcinoma, such as, familial adenomatous polyposis (formerly called Gardner’s syndrome), Carney complex, Cowden’s syndrome, and multiple endocrine neoplasia (MEN) types 2A or 2B; 3) evidence of other thyroid cancer–associated diseases or syndromes, such as hyperparathyroidism, pheochromocytoma, marfanoid habitus, and mucosal neuromas (MEN2B), which make the presence of medullary thyroid cancer more likely; or 4) the presence of suspicious findings detected with imaging, such as focal FDG (18-fluorodeoxyglucose) uptake on PET, or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.\textsuperscript{31}

**Initial Workup**

FNA of the nodule and clinically suspicious lymph nodes is recommended as the first diagnostic test in a clinically euthyroid patient before any imaging studies are performed.\textsuperscript{13} 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 performed during the initial office visit. Recent data show that higher TSH levels are associated with risk for differentiated thyroid cancer.\textsuperscript{32}

Some clinicians, especially in Europe,\textsuperscript{33} recommend obtaining serum calcitonin levels from all patients with thyroid nodules. However, controversy surrounds the cost-effectiveness of this practice in the United States, especially in the absence of confirmatory pentagastrin stimulation testing, and the assumptions used in cost-effective analyses. The American Thyroid Association is equivocal about measuring serum calcitonin.\textsuperscript{3,34} A recent study showed that calcitonin screening may be cost-effective in the United States.\textsuperscript{35} However, false-positive calcitonin readings that can result from minimal elevations can only be ruled out with pentagastrin testing, and pentagastrin is not available in the United States. Ultrasound of the thyroid and central neck is also recommended,\textsuperscript{36} and can also be performed on the lateral neck (category 2B).

Cytologic examination of an FNA specimen is typically categorized as 1) carcinoma (papillary, medullary, or anaplastic) or suspicious for malignancy; 2) follicular or Hurthle cell neoplasm; 3) follicular lesion of undetermined significance; 4) thyroid lymphoma; 5) benign (i.e., nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto’s thyroiditis); or 6) insufficient biopsy (nondiagnostic) (see page 1231). These diagnostic categories for
FNA results reflect the NCI’s State-of-the-Science Conference held in 2007.\textsuperscript{37}

Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in diagnosing thyroid disorders. Although FNA is a very sensitive test, particularly for papillary carcinoma, false-negative results are sometimes obtained; therefore, a reassuring FNA should not override concerns in the presence of worrisome clinical findings.\textsuperscript{38} Hürthle cell neoplasms can sometimes mimic medullary carcinoma cytologically and on frozen section. Discriminating between anaplastic thyroid cancer and other primary thyroid malignancies (e.g., medullary carcinoma, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid can sometimes be difficult.\textsuperscript{39} Metastatic renal carcinoma can mimic a follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma of the thyroid (http://thyroidfna.cancer.gov/pages/conclusions/).

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens. The NCCN Thyroid Carcinoma Panel supports pathology synoptic reports from the College of American Pathologists (CAP) and the Association of Directors of Anatomic and Surgical Pathology (ADASP). Some pathologists currently use a modified format that is believed to comply with both of these synoptic reports. Although no ADASP checklist has been published for thyroid carcinoma, the CAP protocol information and checklists (updated in October 2009) can be accessed on the CAP Web site (http://www.cap.org).

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 protocol checklist complies with the COC requirements.

FNA is far less able to discriminate follicular and Hürthle cell carcinomas from benign adenomas, because diagnosis of these malignancies requires demonstration of vascular or capsular invasion.\textsuperscript{25} Thus, follicular and Hürthle cell carcinomas are rarely diagnosed on FNA.\textsuperscript{18,40} Nodules that yield an abundance of follicular cells with little or no colloid are nearly impossible to categorize as benign or malig-

nant based on FNA. Surgical biopsy is advisable, because approximately 20% of these lesions are follicular carcinomas.\textsuperscript{29} 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 \textsuperscript{131}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.\textsuperscript{41}

Clinically euthyroid patients with a low TSH and a hot nodule on thyroid imaging should be evaluated and treated for thyrotoxicosis as indicated, even when cytology is suspicious for follicular neoplasm; those with a “cold” nodule should proceed to surgery (see page 1231).\textsuperscript{2,3} Patients with a high or normal TSH and cytology suspicious for follicular or Hürthle cell neoplasm should undergo diagnostic lobectomy. Total thyroidectomy should be considered for bilateral disease, unilateral disease greater than 4 cm (especially in men), or if the patient prefers this approach.

An FNA that yields insufficient cellular material for diagnosis and is solid should be repeated, because approximately 50% of subsequent specimens are adequate to assign a diagnosis.\textsuperscript{29} In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may have malignant nodules.\textsuperscript{32} Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of growth.\textsuperscript{29}

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 with follicular or Hürthle cell carcinoma have tumors that aggressively invade structures in the neck or have produced distant metastases. These cancers are difficult to cure.

**Recurrence of Differentiated Thyroid Carcinoma**

Depending on initial therapy and other prognostic variables, approximately 30% of patients with differentiated thyroid carcinoma have tumor recurrences during several decades; 66% of these recurrences
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occur within the first decade after initial therapy.\textsuperscript{13} Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.\textsuperscript{43,44} In one large study, central neck recurrences were seen most often in the cervical lymph nodes (74%), followed by the thyroid remnant (20%), and then the trachea or muscle (6%). Of the group with local recurrences, 8% eventually died of cancer.\textsuperscript{13} 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.\textsuperscript{13}

**Age, Stage, and Sex at Diagnosis**

Although many factors influence the outcome of patients with papillary and follicular thyroid carcinomas, patient age at the time of initial therapy and tumor stage are important.\textsuperscript{13,45–47} Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in men. Thyroid carcinoma is more lethal in patients older than 40 years, and is increasingly so with each subsequent decade of life. The mortality rate increases dramatically after age 60 years (see Figure 1; available online, in these guidelines, at www.NCCN.org [MS-29]). However, tumor recurrence shows a remarkably different behavior with respect to age. Recurrence frequencies are highest (40%) among patients younger than 20 or older than 60 years, whereas at other ages it occurs in only approximately 20% of patients.\textsuperscript{13,45–46} 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 experience more tumor recurrences after therapy than adults, but their prognosis for survival is good.\textsuperscript{49,50} Although the prognosis of children with thyroid carcinoma is favorable for long-term survival (90% at 20 years), the standardized mortality ratio is 8-fold higher than predicted.\textsuperscript{51} Some authors believe that young age affects survival so favorably 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.\textsuperscript{52–54} However, most treating physicians believe that tumor stage and its histologic features should be as significant as patient age in determining management.\textsuperscript{13,49,55,56}

Prognosis is less favorable in men, but the difference is usually small.\textsuperscript{13,54} One study found that gender was an independent prognostic variable for survival and that the risk for death from cancer was approximately twice as high in men as in women.\textsuperscript{13} Because of this risk factor, men with thyroid carcinoma, especially those older than 40 years, may be regarded with special concern.\textsuperscript{57}

**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.\textsuperscript{58,59} Microscopic familial papillary thyroid carcinoma tends to be multifocal and bilateral, often with vascular invasion, lymph node metastases, and high rates of recurrence and distant metastases.\textsuperscript{60} Other familial syndromes associated with papillary thyroid carcinoma are familial adenomatous polyposis,\textsuperscript{61} Carney complex (multiple neoplasia and lentigines syndrome, which affects endocrine glands),\textsuperscript{62} and Cowden’s syndrome (multiple hamartomas).\textsuperscript{63} The prognosis for all of these syndromes is not different from that for spontaneously occurring papillary thyroid carcinoma.

**Tumor Variables Affecting Prognosis**

Some tumor features have a profound influence on prognosis.\textsuperscript{48,64–66} The most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, BRAF mutation status, and metastases.

**Histology:** Although survival rates with typical papillary carcinoma are good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors.\textsuperscript{1} A well-defined tumor capsule, which is found in approximately 10% of papillary thyroid carcinomas, is a particularly favorable prognostic indicator. A worse prognosis is associated with 1) anaplastic tumor transformation; 2) tall-cell papillary variants, which have a 10-year mortality of up to 25%; 3) columnar variant papillary carcinoma (a rapidly growing tumor with a high mortality rate); and 4) diffuse sclerosing variants, which infiltrate the entire gland.\textsuperscript{18,67} Follicular-variant papillary thyroid carci-
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Papillary carcinomas smaller than 4 cm (FVPTC), which is recognized by its follicular architecture and typical papillary cytology, does not seem to have a worse prognosis than the pure papillary lesions if the FVPTC is encapsulated.\(^{38,67-69}\)

Follicular carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It usually has a microfollicular histologic pattern, and is identified as cancer through follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.\(^{70}\) 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 cause death.\(^{71}\) 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 (see page 1231). Cancer may be diagnosed only after thyroidectomy and when 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.\(^{72}\) The poor prognosis is closely related to the patient’s older age at diagnosis, advanced tumor stage, and larger tumor size.\(^{13}\)

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, small, and minimally invasive. Papillary and follicular carcinomas have far less favorable outcomes if they are highly invasive or develop distant metastases.\(^{13,72}\) Staging for patients with papillary and follicular carcinoma who are older than 45 years was revised in the 2002 guidelines (6th edition) from the American Joint Commission on Cancer (AJCC; available online, in these guidelines, at www.NCCN.org [ST-1]).\(^{73}\) Note that new staging guidelines from the AJCC (7th edition) were effective after January 1, 2010, and will be reflected in the 2011 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma (available at www.NCCN.org).\(^{74}\) Many studies (including those discussed in this manuscript) have used AJCC-TNM staging from earlier editions, such as the 5th edition,\(^{75}\) and not the 6th or 7th editions.\(^{73,74}\)

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 WHO classification considers it a variant of follicular carcinoma.\(^{76}\) Molecular studies suggest, however, that this tumor may be more similar to papillary than follicular carcinomas.\(^{77}\) Benign and malignant Hürthle cell tumors usually cannot be discriminated by FNA or frozen section examination, although large (> 4 cm) tumors are more likely to be malignant than smaller ones.\(^{70}\) Hürthle cell carcinomas may be aggressive, especially when vascular invasion or large tumors occur in older patients.\(^{79,80}\) Some believe these cancers are not much more aggressive than similarly staged follicular carcinomas without Hürthle cells.\(^{81}\) In the National Cancer Data Base report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.\(^{12}\)

In 2 large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, approximately twice the frequency of follicular carcinoma metastases.\(^{82,83}\) Fewer Hürthle cell carcinomas concentrate \(^{13}\)I compared with papillary or follicular carcinomas. In a series of 100 patients with distant metastases, \(^{13}\)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.\(^{74}\)

**Primary Tumor Size:** Papillary carcinomas smaller than 1 cm, termed incidentalomas or microcarcinomas, are typically found incidentally after surgery for benign thyroid conditions. Their recurrence and cancerspecific mortality rates are near zero.\(^{85}\)

Other small papillary carcinomas become clinically apparent. For example, approximately 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,\(^{86}\) which may be the presenting feature and also may be associated with distant metastases.\(^{85}\) Otherwise, small (< 1.5 cm) papillary or follicular carcinomas confined to the thyroid almost never cause distant metastases. Furthermore, recurrence rates after 30 years are one third of those
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. Approximately 50% of these metastases are present at diagnosis. Distinct metastases occur even more often in patients with Hurthle cell cancer (35%) and those diagnosed after age 40 years. The sites of reported distant metastases among 1231 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%). The main predictors of outcome for patients with distant metastases are patient age and the tumor's metastatic site, ability to concentrate on chest radiograph, and morphology.

Although some patients, especially younger ones, with distant metastases survive for decades, approximately 50% die within 5 years regardless of tumor histology. 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 disease-free at 10 years, whereas no patients with skeletal metastases survived that long. The survival rates are highest in young patients with diffuse lung metastases seen only on imaging and not on radiograph, which seems to be the most important feature governing an improved survival rate and prolonged disease-free interval with lung metastases. Prognosis is worse with large pulmonary metastases that do not concentrate on radiographs but that do concentrate on imaging.

### 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. When applied to the papillary carcinoma data from the Mayo Clinic, 4 of the schemes that use age—EORTC, TNM 5th edition (tumor, node, metastasis), AMES (age, metastases, extent, and size), and AGES (age, tumor grade, extent, and size)—were effective in separating patients at low-risk (in whom the 20-year, cancer-specific mortality was 1%) from those at high-risk (in whom the 20-year, cancer-specific mortality was 30%–40%). However, in patients with incrementally worsening MACIS (metastasis, age, completeness of resection, invasion, and size) scores of less...
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than 6, 6 to 6.99, 7 to 7.99, and 8 or more, the 20-year survival rates decreased from 99% to 89%, 56%, and 24%, respectively.\(^{23}\) Notably, 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 5 different prognostic paradigms found that some patients in the lowest risk group from each approach died of cancer.\(^{35}\) This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.\(^{73,99}\) The AJCC TNM staging approach (see Table 1; available online, in these guidelines, at www.NCCN.org [ST-1]), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 45 years as stage I or II, even those with distant metastases. Although it predicts cancer mortality reasonably well,\(^{103,104}\) TNM staging was not established to predict recurrence and therefore does not accurately forecast the recurrences that often occur in patients who develop thyroid cancer when they are young. Two studies have shown the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.\(^{46,102}\)

Differentiated thyroid cancer staging systems are of value in epidemiology studies and as tools to stratify patients for prospective trials.\(^{103}\) Staging systems, which are designed to segregate patients based on survival, offer gross indications of prognosis for groups of patients but are probably less useful in determining treatment for individual patients. When treating differentiated thyroid cancer, to which most patients do not succumb, many clinicians have emphasized potential morbidity more than 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. These NCCN Guidelines do not use TNM stages to guide therapy, but instead, many tumor and patient characteristics play important roles in the recommendations. Many specialists in thyroid cancer also follow this paradigm.

Surgical Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total Thyroidectomy:
The continuing debate surrounding the appropriate extent of thyroid resection reflects the limitations of prognostic scoring\(^{54}\) and the morbidity often associated with total thyroidectomy performed outside of referral centers. Patients treated at the Mayo Clinic for low-risk papillary thyroid carcinomas (MACIS score ≤ 3.99) showed no improvement in survival rates after undergoing procedures more extensive than ipsilateral lobectomy; thus, Hay et al.\(^{105}\) concluded that more aggressive surgery was indicated only for those with higher MACIS scores. However, cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy were assessed in patients with papillary carcinoma considered to be low risk according to AMES criteria.\(^{105}\) No significant differences were found in cancer-specific mortality or distant metastasis rates between the 2 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. Based on these observations, Hay et al.\(^{105}\) concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk papillary carcinoma.

Most NCCN panel members (and other authors) advise total thyroidectomy for all patients prospectively diagnosed with thyroid carcinoma,\(^{3,18,106}\) because these procedures are associated with improved disease-free survival, even in children and adults with low-risk tumors.\(^{43,56,105,107}\) Some centers report that patients treated with lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe,\(^{48,104}\) with an overall long-term recurrence rate of more than 30% (compared with 1% after total thyroidectomy and \(^{131}\)I therapy)\(^{13}\) and the highest frequency (11%) of subsequent pulmonary metastases.\(^{108}\) Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for more complete initial thyroid resection.\(^{13}\)

However, some prominent thyroid cancer specialists (including some at NCCN Member Institutions) oppose this view and advocate unilateral lobectomy for most patients with papillary and follicular thyroid carcinoma based on both the low mortality among patients categorized as low risk according to the AMES and other prognostic classification schemes (i.e., most patients), and the high complication rates reported with more extensive thyroidectomy.\(^{53,98,109}\) The large thyroid remnant after unilateral lobectomy, however, may compli-
cating long-term follow-up with serum thyroglobulin (Tg) determinations and whole-body 131I imaging. In most clinical settings, decisions about the extent of thyroidectomy should be individualized and made together with the patient. Circumstances in which unilateral thyroidectomy is inadvisable are detailed in the NCCN Guidelines for Thyroid Carcinoma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

NCCN panelists believe that total lobectomy alone is adequate treatment for papillary microcarcinomas if 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.13,85 The same is true for minimally invasive follicular cancers (see page 1239).

**Completion Thyroidectomy:** Completion thyroidectomy is recommended when remnant ablation is anticipated or if long-term follow-up with serum Tg determinations with or without whole-body 131I imaging is planned, because large thyroid remnants are difficult to ablate with 131I.116 This procedure has a complication rate similar to that of total thyroidectomy. Some experts recommend completion thyroidectomy for routine treatment of tumors 1 cm or larger, because approximately 50% of patients with cancers this size have additional cancer in the contralateral thyroid lobe.88,110–114 In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.111

Miccoli et al.56 found that 61% of irradiated children from Chernobyl who developed thyroid carcinoma treated with lobectomy had unrecognized lung or lymph node metastases that could only be identified after completion thyroidectomy. In another study, patients who underwent completion thyroidectomy within 6 months of their primary operation developed significantly fewer lymph node and hematogenous recurrences, and survived significantly longer than those whose second operation was delayed for more than 6 months.112

**Surgical Complications:** The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur with much higher frequency after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults115 and children undergoing total thyroidectomy. However, the rates of persistent hypocalcemia are reported to be much lower in the hands of experienced thyroid surgeons. In a review of 7 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.117 One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.118

When experienced surgeons perform thyroidectomies, 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 per year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies per year had 4 times as many complications.119

**Radioactive Iodine**

**Adjuvant Radioiodine Therapy:** Postoperative 131I thyroid remnant ablation is performed when a tumor has the potential to recur.120 Studies show decreased recurrence and disease-specific mortality when postoperative 131I therapy is administered as part of the initial treatment, but the supportive data are largely confined to higher-risk populations.13,47,53,121,122 In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was approximately 3-fold higher in patients either treated with thyroid hormone alone or given no postoperative medical therapy when compared with those who underwent postoperative thyroid remnant ablation with 131I (P < .001). Moreover, fewer patients developed distant metastases (P < .002) after thyroid remnant 131I ablation than after other forms of postoperative treatment; however, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter.121 Some experts may find that remnant ablation has a less therapeutic effect because more extensive locoregional surgery had been performed.87

Debate continues about ablating the thyroid bed with 131I after total thyroidectomy.57,121 Proposed mechanisms through 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 posttherapy imaging, which alters disease stage and promotes further patient management. Several other reasons favor remnant ablation: 1) patient follow-up is simplified, because elimination of “thyroid bed” uptake eliminates misinterpretation of it as disease; 2) normal tissue is eliminated as a source of Tg production, which facilitates identification of patients who are disease-free 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 radioactive iodine may be confounded by the accompanying improved specificity of diagnostic testing after elimination of the thyroid remnant, and the possibility that patients who undergo adjuvant therapy may be more likely to undergo more intensive follow-up testing.

**Diagnostic Whole-Body Imaging and Thyroid Stunning:** Whole-body $^{131}$I imaging may be performed (category 2B) after surgery when indicated to assess the completeness of thyroidectomy and whether residual disease is present (see page 1236). However, a phenomenon termed stunning may occur when imaging doses of $^{131}$I induce follicular cell damage. $^{123}$ I Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent $^{131}$I. $^{124}$

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. $^{123-125}$ Some experts recommend that diagnostic $^{131}$I imaging be avoided completely with decisions based on the combination of tumor stage and serum Tg. $^{123}$ Other experts advocate that the whole-body $^{131}$I diagnostic imaging may alter therapy when, for example, unsuspected metastases are identified or an unexpectedly large remnant is identified that requires additional surgery or a reduction in radiiodine dosage to avoid substantial radiation thyroiditis. $^{123,126,127}$

**Administration of Radioiodine Therapy:** Historically, the 3 methods of determining $^{131}$I therapy activities (doses) have included empiric fixed doses, quantitative dosimetry, and upper bound limits that are set by blood dosimetry. $^{123,126}$ Recently a fourth method that adjusts the activity to deliver a selected dose to the blood (as a surrogate of the activity available for the remnant or target tissue) became available using simplified single–time point whole-body dosimetry (Kloos, personal communication).

Previously, hospitalization was required for administering therapeutic doses of $^{131}$I larger than 30 mCi (1110 MBq). However, this 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. $^{128}$

**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 may be treated with approximately 100 to 175 mCi (3700–6475 MBq) of $^{131}$I. Cancer growing through the thyroid capsule and incompletely resected is treated with 150 to 200 mCi (5550–7400 MBq). Patients with distant metastases are usually treated with 200 mCi (7400 MBq) of $^{131}$I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in elder patients and those with impaired kidney function. $^{129,130}$ Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of $^{131}$I (which is very uncommon) are treated with 150 mCi (5550 MBq) of $^{131}$I or less to avoid lung injury, which may occur when more than 80 mCi remain in the whole body 48 hours after treatment. The administered activity of radioiodine therapy should be adjusted for pediatric patients.

**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. This approach is attractive, because radiation exposure from arbitrarily fixed doses of $^{131}$I can vary substantially. When the calculated dose to the tumor is less than 3500 cGy, the cancer is unlikely to respond to $^{131}$I therapy. $^{128,131}$ 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 neces-
sary 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 diffuse pulmonary uptake is present. Thyroid cancer dosimetry and radiiodine therapy with doses more than 200 mCi are best performed in medical centers with experience using these treatments.

Posttreatment $^{131}$I Imaging: When $^{131}$I therapy is given, whole-body radioiodine imaging should be performed several days later to document $^{131}$I uptake by the tumor, primarily because up to 25% of this imaging shows lesions that may be clinically important that were not detected on the diagnostic imaging. A study of pre- and posttreatment imaging showed that these differed in 27% of the treatment cycles, but only 10% of the posttreatment imaging showed clinically significant new foci of metastatic disease. Posttreatment imaging was most likely to reveal clinically important new information in patients younger than 45 years who had previously undergone $^{131}$I therapy. Conversely, in older patients and patients who had not previously undergone $^{131}$I therapy, posttreatment imaging rarely yielded new information that might have altered the patient’s prognosis. Thus, the panel only gives a category 2B recommendation for posttreatment radiiodine imaging.

Assessment and Management After Initial Treatment

Serum Tg determinations, neck ultrasound, and whole-body $^{131}$I imaging detect recurrent or residual disease in most patients who have undergone total thyroid ablation. In contrast, neither serum Tg or whole-body radiiodine imaging is specific for thyroid cancer in patients who have not undergone thyroidectomy and remnant ablation. When initial ablative therapy has been completed, serum Tg should be measured periodically. Serum Tg can be measured while the patient is taking thyroxine, but the test is more sensitive when thyroxine has been stopped or when recombinant human TSH (rhTSH) is given to increase the serum TSH.

Using current Tg assays, patients with measurable serum Tg levels during TSH suppression and those with stimulated Tg levels more than 2 ng/mL are likely to have residual/recurrent disease that may be localized promptly in almost 50% of patients and over the next 3 to 5 years in an additional 30%. Approximately 6% of patients with detectable serum Tg levels, which are less than 2 ng/mL after stimulation, experience recurrences over the next 3 to 5 years, whereas this is true for approximately 2% of patients with completely undetectable serum Tg after stimulation. Conversely, the long-term clinical significance is uncertain for disease only detected through minimally elevated Tg levels after stimulation.

rhTSH: During follow-up, periodic withdrawal of thyroid hormone therapy traditionally has been required to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements (with or without $^{131}$I imaging) could be performed to detect residual thyroid tissue or carcinoma. An alternative to thyroid hormone withdrawal is the administration of rhTSH intramuscularly, which stimulates thyroidal $^{131}$I uptake and Tg release while the patient continues thyroid hormone suppressive therapy and avoids symptomatic hypothyroidism.

A second multicenter international study was performed to assess the effects of 2 rhTSH dosing schedules on whole-body $^{131}$I imaging and serum Tg levels when compared with imaging and Tg levels obtained after thyroid hormone withdrawal. The imaging method in this study was more carefully standardized and accounted for the fact that $^{131}$I retention was higher in patients rendered hypothyroid than in patients given rhTSH. Imaging was concordant in 89% of the patients and superior in 4% after rhTSH, 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 rhTSH-stimulated whole-body imaging and serum Tg measurements detected 100% of metastatic carcinoma. In this study, 0.9 mg of rhTSH was given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of $^{131}$I on the third day. Whole-body imaging and Tg measurements were performed on the fifth day. Whole-body $^{131}$I images were acquired after 30 minutes of imaging or after obtaining 140,000 counts, whichever came first. A serum Tg of 2.0 ng/mL or higher obtained
72 hours after the last rhTSH injection indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole-body imaging findings.\textsuperscript{136,139} rhTSH is well tolerated. Nausea (10.5\%) and transient mild headache (7.3\%) are its main adverse effects.\textsuperscript{136} It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.\textsuperscript{138}

**Measuring Serum Tg:** Serum Tg measurement is the best means of detecting thyroid tissue. Tg should be measured when TSH has been stimulated either by thyroid hormone withdrawal or by rhTSH, when serum Tg has a lower false-negative rate than whole-body \textsuperscript{131}I imaging.\textsuperscript{135–137,140} Serum Tg levels vary in response to the increase in serum TSH after thyroid hormone withdrawal or rhTSH stimulation. Serum Tg generally does not rise as high after rhTSH administration as after withdrawal of thyroid hormone. The conditions for rhTSH-stimulated whole-body \textsuperscript{131}I imaging stipulate using 4-mCi \textsuperscript{131}I doses (based on the doses used in the pivotal phase III trial)\textsuperscript{136} and an imaging time of 30 minutes or until 140,000 counts are obtained.

The sensitivity and specificity of various Tg assays, however, vary widely in different laboratories, even with the use of an international standard (CRM 457).\textsuperscript{141,142} Therefore, experts recommend that patients undergo Tg monitoring using the same Tg assay performed in the same laboratory. Ideally, serum is frozen and saved for future analyses if needed, especially if a change in Tg assay is necessary.

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.\textsuperscript{143} These antibodies typically lower the Tg value in immunochemiluminometric (ICMA) and immunoradiometric (IRMA) assays, while raising the value in older radioimmunoassay. Although the clinical importance of these antibodies is unclear, their persistence for more than 1 year or so after thyroidectomy and radioactive iodine ablation probably indicates the presence of residual thyroid tissue and possibly an increased risk for recurrence.\textsuperscript{143} In one study, 49\% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of 100 U/mL or more experienced a recurrence, compared with only 3\% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of less than 100 U/mL.\textsuperscript{144} In patients with coexistent autoimmune thyroid disease at surgery, anti-Tg antibodies may persist much 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.\textsuperscript{145}

Heterophile antibodies may falsely increase or decrease serum Tg measurements in the absence of anti-Tg antibodies. Clues to the presence of a false Tg elevation are the lack of Tg rise with TSH stimulation and the lack of linear results with serum sample dilution. Heterophile blocking tubes may be used to correct this problem.

RNA-based detection strategies, including the sodium–iodine symporter, 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.\textsuperscript{146–149}

**Treating Tg-Positive/Image-Negative Patients:** Posttreatment \textsuperscript{131}I imaging may indicate the location of metastases when the serum Tg level is increased, but a tumor (or metastases) cannot be found by physical examination or other localizing techniques (i.e., diagnostic \textsuperscript{131}I imaging, neck ultrasonography, CT, MRI, or PET). Pulmonary metastases may be found only after administering therapeutic doses of \textsuperscript{131}I and obtaining whole-body imaging within a few days of treatment.\textsuperscript{150} In a study of 283 patients treated with 100 mCi (3700 MBq) of \textsuperscript{131}I, 6.4\% had lung and bone metastases detected after treatment that had been suspected based on high serum Tg concentrations alone but had not been detected after 2-mCi (74 MBq) diagnostic imaging.\textsuperscript{151} In another study in 17 patients with increased serum Tg concentrations and negative 5-mCi (185 MBq) diagnostic imaging, 16 patients showed \textsuperscript{131}I uptake after 75 to 140 mCi (2775–5180 MBq) of \textsuperscript{131}I; more than 50\% of these patients had lung metastases.\textsuperscript{152}

Unfortunately, most diagnostic imaging–negative/Tg-positive patients are not rendered disease-free from \textsuperscript{131}I therapy; however, the tumor burden may be diminished.\textsuperscript{153} Thus, most patients with residual or recurrent disease confined to the neck un-
Thyroid Hormone Suppression of TSH: Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal for treating patients with papillary, follicular, or Hürthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH. In general, patients with known residual carcinoma or those at high risk for recurrence should have their TSH levels maintained near the lower limit of the reference range (either slightly below or slightly above). Patients who remain disease-free for several years can probably have their TSH levels maintained within the reference range. The risk and benefit of TSH-suppressive therapy must be balanced for each individual patient because of the potential toxicities associated with TSH-suppressive doses of levothyroxine, including cardiac tachyarrhythmias (especially in the elderly), bone demineralization (particularly in postmenopausal women), and frank symptoms of thyrotoxicosis. Patients whose TSH levels are chronically suppressed should be counseled to ensure an adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d).

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma are reported by some authors for patients treated with thyroid hormone suppressive therapy. 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 with spontaneously occurring primary hypothyroidism (1.62 mcg/kg per day), and still higher doses are required to suppress serum TSH in patients with thyroid carcinoma. Still, the optimal TSH level to be achieved in patients with thyroid carcinoma is uncertain. Superior outcomes were associated with aggressive thyroid hormone suppression therapy in high-risk patients but were achieved with modest suppression in patients with stage II disease. Excessive TSH suppression (into the undetectable, thyrotoxic range) is not required to prevent disease progression in all patients with differentiated thyroid cancer.

Adjuvant External-Beam RT: No prospective controlled trials have been completed using adjuvant external-beam RT. One retrospective study showed a benefit of adjuvant external-beam RT after radioactive iodine in patients older than 40 years with invasive papillary thyroid cancer (T4) and lymph node involvement (N1). Local recurrence and locoregional and distant failure were significantly improved. A second study showed improved cause-specific survival and local relapse-free rate in selected patients treated with adjuvant external-beam RT (in addition to total thyroidectomy and TSH-suppressive therapy with thyroid hormone) for papillary thyroid carcinoma with microscopic residuum. Not all patients underwent radioactive iodine therapy. Benefit was not shown in patients with follicular thyroid carcinoma or other subgroups of papillary thyroid carcinoma. Similarly, patients with microscopic residual papillary carcinoma after surgery are more commonly rendered disease-free after undergoing external RT (90%) than when they do not (26%). In another study, patients with microscopically invasive follicular carcinoma were also more often disease-free after surgery when postoperative external RT was given (53%) than when it was not (38%); however, these patients had not received radioactive iodine. Similar benefit was shown among patients treated with radioactive iodine alone and those treated with it after surgery.

Chemotherapy, External-Beam Radiation, and Surgical Excision of Metastases: Isolated skeletal...
Thyroid Carcinoma

metastases should be considered for surgical excision or external irradiation. Brain metastases pose a special problem, because \(^{131}\)I therapy may induce cerebrovascular edema. Neurorsurgical resection can be considered for brain metastases. For solitary lesions, either neurorsurgical resection or stereotactic radiosurgery is preferred. Once brain metastases are diagnosed, disease-specific mortality is very high (67%), with one retrospective study showing a reported median survival of 12.4 months. Survival was significantly improved after surgical resection of one or more tumor foci.\(^{165}\)

Life-threatening tumors refractory to all other forms of therapy may be palliatively treated with doxorubicin, although the response rate is poor.\(^{68}\) 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 is mainly used 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 5 chemotherapy protocols, only 2 (3%) patients experienced objective responses.\(^{166}\) In a review of published series, 38% of patients experienced a response (defined as a decrease in tumor mass) to doxorubicin.\(^{167}\) Combination chemotherapy is not clearly superior to doxorubicin therapy alone.\(^{68}\) Overall, traditional cytotoxic systemic chemotherapy (e.g., doxorubicin) has minimal efficacy in patients with metastatic differentiated thyroid disease.

Several phase II trials are evaluating novel treatments for patients with metastatic differentiated thyroid carcinoma. Although 12-month progression-free survival was only 3% in one study assessing celecoxib (400 mg twice daily) in patients with progressive, radioiodine-unresponsive disease,\(^{168}\) 38% of the patients had stable disease, representing a possible alteration in their disease course. Other agents are now in clinical trials, including 1) multitargeted kinase inhibitors, such as motesanib diphosphate (AMG-706),\(^{169,170}\) sorafenib,\(^{171–173}\) sunitinib,\(^{174,175}\) axitinib,\(^{176}\) and vandetanib; 2) the histone deacetylase inhibitors, vorinostat and depsipeptide; 3) the DNA methylation inhibitor, decitabine; 4) the heat-shock protein 90 (HSP-90) inhibitor, 17allylamino-17-demethoxygeldanamycin (17-AAG); 5) the proteasome inhibitor, bortezomib; and 6) a derivative of thalidomide, lenalidomide.\(^{177,178}\) Recent reviews of the completed phase II clinical trials suggest that tyrosine kinase inhibitors have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of subjects, usually for 12 to 24 months.\(^{179,180}\)

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 ultrasound (including lateral neck) is recommended if not previously performed. 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.\(^{181}\) Vocal cord mobility should also be evaluated. A chest radiograph can be considered.

The panel members agreed on the characteristics of patients who require total thyroidectomy and neck dissection (if lymph nodes are palpable or biopsy positive) as the primary treatment (see page 1233). If the nodes are negative, prophylactic central neck dissection can be considered (category 2B) but is not required in all cases.\(^{182–184}\)

Panel members did not agree about the preferred primary surgery for patients who are assumed to be at lower risk for cancer-specific mortality. Most panel members opted for total thyroidectomy (category 2B) in any patient in whom papillary thyroid carcinoma was identified preoperatively or during surgery. However, a few panel members felt strongly that, initially, lobectomy plus isthmusectomy (category 2B) is adequate surgery for patients at lower risk. A study in more than 5000 patients found that survival of patients after partial thyroidectomy was similar to survival after total thyroidectomy for both low- and high-risk patients.\(^{185}\) However, another study in 2784 patients with differentiated thyroid cancer (86% with papillary thyroid cancer) found that total thyroidectomy was associated with increased survival in high-risk patients.\(^{186}\) A more recent study in 52,173 patients found that, compared with lobectomy, total thyroidectomy improves survival in patients with papillary thyroid carcinoma greater than 1 cm.\(^{187}\)

For patients who undergo lobectomy plus isth-
musectomy (lower-risk patients), completion of thyroidectomy is warranted for aggressive variant disease, macroscopic multifocal disease, positive isthmus margins, cervical lymph node metastases, or gross extrathyroidal extension. Aggressive variant disease is defined as tall cell variant, columnar cell, or poorly differentiated features.

The panel agreed that completion of thyroidectomy is appropriate for any large tumor (> 4 cm), positive margins, gross extrathyroidal extension, macroscopic multifocal disease, or confirmed nodal metastases. Incidentally discovered papillary carcinomas measuring 1 to 4 cm may warrant a completion thyroidectomy (category 2B) for an aggressive variant (see page 1234); observation is another option for these patients (i.e., with Tg measurement plus anti-Tg antibodies). The TSH levels of these patients should be suppressed with levothyroxine therapy (see page 1232). Lobectomy is sufficient for tumors resected with negative margins, no contralateral node, no suspicious lymph node, or small (< 1 cm) papillary carcinomas found incidentally on the final pathology sections during thyroid surgery for benign disease; these patients are observed (i.e., with Tg measurement plus anti-Tg antibodies). Levothyroxine therapy to reduce serum TSH to low or low-normal concentrations is recommended for these patients.

Radioactive Iodine
Postoperative Whole-Body ¹³¹I Diagnostic Imaging: Performing diagnostic whole-body ¹³¹I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before ¹³¹I therapy is a category 2B recommendation (see page 1236). The panel advises that this decision be weighed against the problem of stunning that occurs with diagnostic ¹³¹I imaging. ¹³¹I Diagnostic whole-body ¹³¹I imaging does not carry a risk for stunning. The alternatives to performing diagnostic ¹³¹I imaging are to obtain an ¹²³I image before ¹³¹I therapy, obtain a thyroid uptake measurement with microcurie quantities of radiiodine to confirm neck uptake, or forgo diagnostic imaging. If radiiodine is administered after a diagnostic ¹³¹I study, the interval between radiiodine doses should be minimized. Whenever therapeutic radiiodine is administered, whole-body imaging should be obtained 5 to 8 days after treatment with ¹³¹I, which is termed posttreatment ¹³¹I imaging in the guidelines.

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. Adjuvant radiiodine ablation (30–100 mCi) to destroy residual thyroid function is recommended for suspected (based on pathology, postoperative Tg, and intraoperative findings) or proven thyroid bed uptake in patients who have undergone total thyroidectomy and have no gross residual disease in the neck (see page 1236). The administered activity of radioiodine therapy should be adjusted for pediatric patients. The panel does not routinely recommend empiric administration of radiiodine without diagnostic imaging.

Radioactive Iodine Treatment: Therapy with ¹³¹I is advised for patients with tumors found on examination, by imaging studies, or through increased serum Tg levels if the tumors are not amenable to surgical removal and if they concentrate ¹³¹I. All patients should be examined, and palpable neck disease should be surgically resected before any radioiodine treatment. A negative pregnancy test is required before the administration of radioiodine in women of childbearing potential. The panel agrees that radioiodine treatment is not needed for patients with Tg levels less than 1 ng/mL, negative radioiodine imaging, and negative anti-Tg antibodies. For patients with suspected or proven radiodine responsive residual tumor, radioiodine treatment can be given at 100 to 200 mCi along with posttreatment imaging; dosimetry can be considered for distant metastases (see page 1236). Again, the administered activity of radioiodine therapy should be adjusted for pediatric patients.

For unresectable locoregional recurrence, radioiodine treatment with RT can be given if the radioiodine imaging is positive; RT alone is another option in the absence of radiodine uptake. When recurrent disease is suspected based on high stimulated Tg values (> 10 ng/mL) and negative imaging studies (including PET scans), radioiodine therapy can be considered (category 3) using an empiric fixed dose of 100 to 150 mCi of ¹³¹I (see page 1237); however, there was major disagreement about this recommendation. For patients with metastatic disease that is not locoregional, the panel recommends individualized treatment based on the tumor locations (e.g., CNS, bone, or sites other than CNS; see page 1238).
**Adjuvant External-Beam RT**

The guidelines recommend that external RT be considered for patients older than 45 years with T4 (surgically evident gross extrathyroidal extension) and without gross residual disease in their neck (see page 1236).

**Thyroxine Suppression of TSH**

Thyroxine therapy is required after total thyroid resection, and is advisable even after lobectomy and isthmusectomy. The level of TSH suppression is not stipulated, because data currently conflict. Practically, the most appropriate dose of thyroid hormone for most low-risk patients with differentiated thyroid cancer is one that decreases the serum TSH concentration to just below the lower limit of the normal range (see page 1232). 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, including those with metastatic disease. The risk and benefit of TSH-suppressive therapy must be balanced for each patient. Patients whose TSH levels are chronically suppressed should be counseled to ensure an adequate daily intake of calcium (1200 mg/d) and vitamin D (1000 units/d).

**Surveillance and Maintenance**

The guidelines recommend the following for surveillance and maintenance (see page 1237): 1) physical examination, TSH, Tg, and anti-Tg antibody measurements every 6 to 12 months, then annually if patients remain disease-free; 2) periodic neck ultrasound; 3) TSH-stimulated Tg (without radioiodine imaging) in patients previously treated with radioiodine with negative TSH-suppressed Tg and negative anti-Tg antibodies; 4) consider TSH-stimulated radioiodine imaging in patients with T3–4 or M1 at initial staging, or with abnormal Tg levels (either TSH-suppressed or TSH-stimulated), abnormal anti-Tg antibodies, or abnormal ultrasound during surveillance; 5) whole-body 131I imaging every 12 months until no response is seen to radioiodine treatment in iodine responsive tumors (either withdrawal of thyroid hormone or rhTSH) for patients with detectable Tg, distant metastases, or soft tissue invasion on initial staging; and 6) consider additional nonradioiodine imaging (e.g., FDG-PET with or without CT) if Tg levels are ≥ 10 ng/mL for patients whose 131I imaging is negative and stimulated Tg is 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. In selected patients who may be at higher risk for residual or recurrent disease (e.g., those with N1 disease), a stimulated Tg should be obtained and concomitant diagnostic radioiodine (RAI) imaging considered. In patients with a positive stimulated Tg, concomitant RAI imaging may help determine whether treatment with RAI is indicated (i.e., RAI is often beneficial in iodine-avid disease but not in non-iodine avid disease; see page 1237). A subgroup of very–low-risk patients (micro-papillary carcinomas entirely confined to the thyroid gland) may only require periodic ultrasound follow-up, without stimulated Tg or follow-up whole-body imaging, as long as the basal Tg remains low (see page 1237).

**Recurrent and Metastatic Disease**

The panel agrees that the preferred therapy for recurrent disease is surgery if the tumor can be localized and is resectable (see page 1237). Preoperative vocal cord assessment should be considered for those with central neck recurrence. For unresectable locoregional recurrences, 131I therapy is recommended for tumors that concentrate 131I (i.e., radioiodine imaging–positive), and external-beam RT alone is recommended for those that do not (i.e., radioiodine imaging–negative). Unresectable iodine-responsive locoregional disease that is unlikely to respond to radioiodine therapy alone may also be treated with external-beam RT.

For metastatic disease, several therapeutic approaches are recommended (see page 1238), depending on the site and number of tumor foci. Patients should continue to receive levothyroxine to suppress TSH levels. For skeletal metastases, surgical palliation is recommended for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are 131I treatment (if the radioiodine imaging is positive) with consideration of dosimetry to maximize dosing and/or external-beam RT. Intravenous bisphosphonate (pamidronate or zoledronic acid) therapy may be considered for symptomatic bone metastases, and embolization of metastases can also be considered. For metastases to the CNS, neurosurgical resection should be
considered for appropriate cases, and/or radioiodine treatment (with rhTSH and steroid prophylaxis) if the radioiodine imaging is positive (with consideration of dosimetry to maximize dosing), and/or image-guided RT (see page 1238). For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred.

For sites other than the CNS, surgical resection and/or RT of selected, enlarging, or symptomatic metastases can be considered, and/or 131I is recommended if the tumor concentrates the radioisotope (with consideration of dosimetry to maximize the dosing). For clinically progressive or symptomatic disease, patients should consider 1) clinical trials; 2) small molecule kinase inhibitors (i.e., sorafenib or sunitinib) or systemic therapy if a clinical trial is not available; or 3) best supportive care. Because chemotherapy has been generally disappointing, the guidelines recommend clinical trials for non–radioiodine avid tumors; sorafenib, sunitinib, or traditional cytotoxic systemic therapy can be considered if a clinical trial is not available. Several agents are currently being investigated in clinical trials (http://www.thyroidtrials.org, http://www.nci.nih.gov клиничалных trials).

**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. The diagnosis of follicular carcinoma requires evidence of invasion through the capsule of the nodule. Thus, FNA is not specific for follicular thyroid carcinoma (unlike papillary carcinoma) and accounts for the main differences in management of the 2 tumor types. The FNA cytologic diagnosis of follicular neoplasm is 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.

Because most patients with follicular neoplasms have benign disease, total thyroidectomy is recommended only if invasive cancer or metastatic disease is apparent at surgery or if the patient chooses 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 (see page 1239).

Completion thyroidectomy is also recommended 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. These tumors may also be simply observed carefully, because minimally invasive follicular carcinomas have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma occur occasionally. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see page 1242).

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 (i.e., T4). However, RT is used for unresectable gross residual disease in the neck. As for papillary carcinoma, adjuvant radioiodine ablation to destroy residual thyroid function is recommended for suspected or proven thyroid bed uptake. Radioiodine treatment and posttreatment imaging (with consideration of dosimetry for distant metastasis) may be administered for suspected or proven radioiodine responsive residual tumor (see page 1241). The decision to perform diagnostic whole-body 131I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before 131I therapy is administered is a category 2B recommendation for both follicular and papillary carcinoma.

**Hürthle Cell Carcinoma**

A Hürthle cell 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. The management of this Hürthle cell (oxyphilic)
carcinoma is almost identical to follicular carcinoma, except that 1) locoregional nodal metastases occur frequently, and therefore therapeutic compartment lymph node dissections may be needed for positive nodes, or prophylactic (category 2B) central neck compartment dissection may be considered for negative nodes; and 2) metastatic Hürthle cell tumors are less likely to concentrate $^{131}$I. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see page 1247).

Adjuvant RT can be considered postoperatively for advanced Hürthle cell lesions (i.e., T4; see page 1246), similar to the management for papillary carcinoma. Nonetheless, adjuvant radioiodine therapy has been reported to decrease the risk for locoregional recurrence and is recommended for unresectable disease with positive radioiodine imaging. Radioiodine therapy (100–150 mCi) should be considered (category 2B) after thyroidectomy for patients with stimulated Tg levels of more than 10 ng/mL who have negative scans (including FDG-PET; see page 1247).80 The panel recommends (category 2B) that diagnostic whole-body $^{131}$I imaging with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) be performed before $^{131}$I therapy is administered. However, patients with clinical indications for radioiodine therapy (suspection based on pathology, postoperative Tg, and intraoperative findings) may not require imaging (category 2B; see page 1246). Postoperative RT may be used for advanced lesions.

### Medullary Thyroid Carcinoma

Medullary thyroid carcinoma was previously published in this journal (May 2010). A complete discussion of thyroid carcinoma, including medullary thyroid carcinoma, is available online on the NCCN Web site (www.NCCN.org).

### Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.193 Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.194 Fewer than 10% of patients are younger than 50 years, and 60% to 70% of patients are women.45,194 The incidence of anaplastic carcinoma is decreasing.193

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 de-differentiating steps, particularly loss of the p53 tumor suppressor protein.195 No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, radioiodine imaging cannot be used and radioiodine treatment is not effective in these patients.

Patients with anaplastic carcinoma present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.190,196 The lungs and pleura are the most common site of distant metastases, being present in up to 90% of patients with distant disease. Approximately 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; available online, in these guidelines, at www.NCCN.org [ST-1]). The T4 category includes T4a tumors, which are intrathyroidal and surgically resectable, and T4b tumors, which are extrathyroidal and not surgically resectable. However, clinically apparent anaplastic tumors are usually unresectable.

The diagnosis of anaplastic carcinoma is usually established through core or surgical biopsy. However, discriminating between anaplastic thyroid cancer and other primary thyroid malignancies (i.e., medullary thyroid carcinoma, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid can occasionally be difficult.39 Diagnostic procedures include a complete blood cell count, serum calcium, and TSH level. CT scans of the neck can accurately determine the extent of the thyroid tumor and can identify tumor invasion of the great vessels and upper aerodigestive tract structures.197 CT images of the head, chest, abdomen, and pelvis are used to establish the extent of distant metastases. Bone scans and FDG-PET scans can be considered. Bone metastases are usually lytic.
Treatment and Prognosis

No effective therapy exists for anaplastic carcinoma, and the disease is almost uniformly fatal. The median survival from diagnosis ranges from 3 to 7 months. 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. 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 attempted complete tumor resection has not been shown to prolong survival. External-beam RT can increase short-term survival in some patients; RT can also improve local control and can also be used for palliation (e.g., to prevent asphyxiation). Treatment with single-drug chemotherapy also does not improve survival or disease control in the neck, although perhaps 20% of patients experience some response in distant metastases. The introduction of hyperfractionated RT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to approximately 80%, with subsequent median survival of 1 year. Distant metastases then become the leading cause of death. Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin, followed by debulking surgery in patients with responsive disease. However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or survival. Paclitaxel has been tested in newly diagnosed patients and may provide some palliative benefit.

Once the diagnosis of anaplastic carcinoma is confirmed pathologically, the panel recognizes the importance of rapidly determining the potential for local resection. If the disease is deemed likely to be resectable, an attempt at total thyroidectomy should be made, with selective resection of all involved local or regional structures and nodes. The patency of the airway should be considered throughout the patient’s course. Given the poor outcome with current standard therapy, all patients, regardless of surgical resection, should be considered for clinical trials. Currently, ongoing clinical trials include combrestatin A4 phosphate (CA4P; a vascular disrupting agent), CS-7107 (an oral PPAR gamma [peroxisome proliferator–activated receptors] agonist), and novel multitargeted therapies, including bevacizumab with doxorubicin, sorafenib, sunitinib, and imatinib (http://clinicaltrials.gov/ct2/results?term=thyroid+ca
cer). A patient with anaplastic thyroid cancer had a durable complete response in a phase I trial with CA4P, and has been disease-free for more than 3 years. Recent data using fosfotubulin, which is another vascular disrupting agent, in 26 patients with advanced anaplastic thyroid cancer showed that 33% of patients survived more than 6 months.

Multimodality therapy should also be considered. Although optimal results have been reported with hyperfractionated RT combined with chemotherapy, the panel acknowledged that considerable toxicity is associated with this treatment and that prolonged remission is uncommonly reported. A recent study found that surgery and RT were associated with improved survival, but not chemotherapy. 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.

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<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
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<tr>
<td>Douglas W. Ball, MD, MD</td>
<td>Eisai Inc.; and Exelixis Inc.</td>
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<td>1/7/10</td>
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<td>David Byrd, MD, MD</td>
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<td>10/7/09</td>
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<tr>
<td>Raza A. Dilawari, MD, MD</td>
<td>None</td>
<td>Eisai Inc.; Pfizer Inc.; and Schering-Plough Corporation</td>
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<td>Gerard M. Doherty, MD, MD</td>
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<td>Quan-Yang Duh, MD, MD</td>
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<tr>
<td>Hormoz Ehya, MD, MD</td>
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<td>Molecular Insight</td>
<td>Molecular Insights Pharmaceuticals</td>
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<td>Richard T. Kloos, MD, MD</td>
<td>Bayer HealthCare; Eisai Inc.; Exelixis Inc.; Onyx Pharmaceuticals, Inc.; Diagnostic Hybrids; and Veracyte</td>
<td>AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Genzyme Corporation; and Onyx Pharmaceuticals, Inc.</td>
<td>None</td>
<td>American Thyroid Association</td>
<td>3/31/10</td>
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Dr. Hughes has disclosed that she has a patent, equity, or royalty in Myriad Genetic Laboratories, Inc.; Affymetrix; and Qiagen NV. The remaining guidelines staff have disclosed that they have no conflicts of interest.