National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Thyroid Carcinoma

V.1.2008

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

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

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines updates

Summary of changes in the 1.2008 version of the Thyroid Carcinoma Guidelines from the 2.2007 version include:

Thyroid Nodule Evaluation

THYR-1

- MEN2 replaced hyperparathyroidism under the listing of diseases associated with thyroid cancer.
- The central and neck compartments were added to ultrasound in the workup section with a category 2B designation.
- A simple cyst was added to the characteristics of nodules that only require clinical follow-up.
- The recommendation to consider a lateral neck ultrasound was added to the follow-up recommendations for non-suspicious nodules or nodules < 1 cm.

THYR-2

- Footnote "d" was added stating that follicular and Hurthle cell carcinoma are rarely diagnosed on FNA.
- Footnote "g" was added to define benign characteristics.

Papillary Carcinoma

PAP-1

- When nodes are positive by ultrasound or FNA cytology after a thyroidectomy, a lateral neck dissection is recommended for levels II-IV. Level V was previously included and now is listed as "consider".
- If nodes are negative after a thyroidectomy, "consider prophylactic neck dissection" was added with a category 2B recommendation.

PAP-4

- "with negative antibodies" was added to "Thyroglobulin < 1 ng/mL and radioiodine scan negative".

PAP-5

- Bullet 2 - footnote "f" is new to the page describing the subgroup of patients who are low risk and may not require an ultrasound.
- Bullet 4 - the recommendation for radioiodine scan was changed from "until no radioactive iodine avid tumor is evident" to "until no response is seen to RAI treatment in iodine avid tumors".
- Footnote "h" is new to the page recommending preoperative vocal cord assessment if central neck recurrence.

PAP-6

- Footnote "i" describing the surgical approach and footnote "j" that "whole brain RT is not included" are new to the page.
- The qualifier of "for progressive or symptomatic disease" was added to the systemic therapy option for any extracervical sites.
- Sorafenib was also added as a treatment option for any extracervical sites.

Follicular Carcinoma

FOLL-1

- When nodes are positive after a thyroidectomy, a lateral neck dissection is recommended for levels II-IV. Level V was previously included and now is listed as "consider".

FOLL-3

- "with negative antibodies" was added to "Thyroglobulin < 1 ng/mL and radioiodine scan negative".

FOLL-4

- Bullet 2 - footnote "d" is new to the page describing the subgroup of patients who are low risk and may not require an ultrasound.
- Bullet 4 - the recommendation for radioiodine scan was changed from "until no radioactive iodine avid tumor is evident" to "until no response is seen to RAI treatment in iodine avid tumors".
- Footnote "f" is new to the page recommending preoperative vocal cord assessment if central neck recurrence.

FOLL-5

- Footnote "g" describing the surgical approach and footnote "h" that "whole brain RT is not included" are new to the page.
- The qualifier of "for progressive or symptomatic disease" was added to the systemic therapy option for other extracervical sites.

Continue

Summary of the Guidelines updates

Summary of changes in the 1.2008 version of the Thyroid Carcinoma Guidelines from the 2.2007 version include:

Hürthle Cell Carcinoma

HÜRT-1

- When nodes are positive after a thyroidectomy, a lateral neck dissection is recommended for levels II-IV. Level V was previously included and now is listed as "consider".
- If nodes are negative after a thyroidectomy, "consider prophylactic neck dissection" was added with a category 2B recommendation.
- The recommendations for management of Hürthle cell neoplasm were changed to: "diagnostic lobectomy/isthmusectomy and consider total thyroidectomy for high risk patients (large tumors)."

HÜRT-3

- "with negative antibodies" was added to "Thyroglobulin < 1 ng/mL and radioiodine scan negative".

HÜRT-4

- Bullet 2 - footnote "e" is new to the page describing the subgroup of patients who are low risk and may not require an ultrasound.
- Bullet 4 - the recommendation for radioiodine scan was changed from "until no radioactive iodine avid tumor is evident" to "until no response is seen to RAI treatment in iodine avid tumors".
- Footnote "g" is new to the page recommending preoperative vocal cord assessment if central neck recurrence.

HÜRT-5

- Footnote "h" describing the surgical approach and footnote "i" that "whole brain RT is not included" are new to the page.
- The qualifier of "for progressive or symptomatic disease" was added to the systemic therapy option for other extracervical sites.

Medullary Carcinoma

MEDU-1

- "Consider genetic counseling" was added as a recommendation in the workup section.
- "Consider" was removed from the recommendation for neck ultrasound.
- "Consider" was added to the recommendation for contrast-enhanced CT of the chest and mediastinum.

MEDU-2

- "Consider" was removed from the recommendation for neck ultrasound.

MEDU-3

- "Calcium" was added to the recommendation "Measure serum intact parathyroid hormone"
- "Suppressed" was changed to "No primary hyperparathyroidism" and "Not suppressed" was changed to "Primary hyperparathyroidism".
- The qualifier "if mutation identified after age 5" was added after the recommendation for "total thyroidectomy by age 5 or when mutation identified".

MEDU-5

- Sorafenib was added as a treatment option for disseminated symptomatic disease.

Nodule Evaluation

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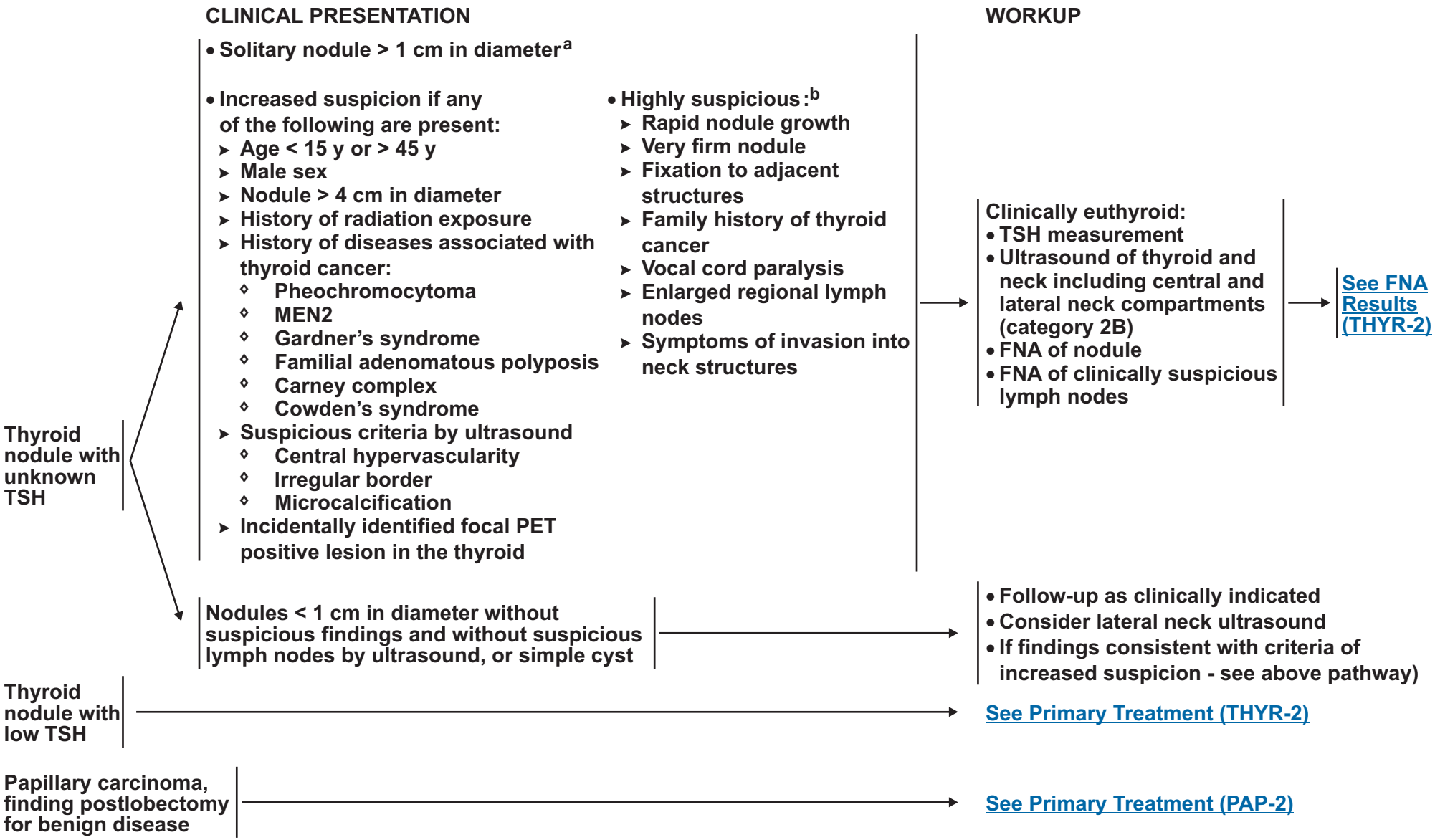
Thyroid Carcinoma TOC
Staging, Discussion, References



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

[b] Consider surgery after FNA.

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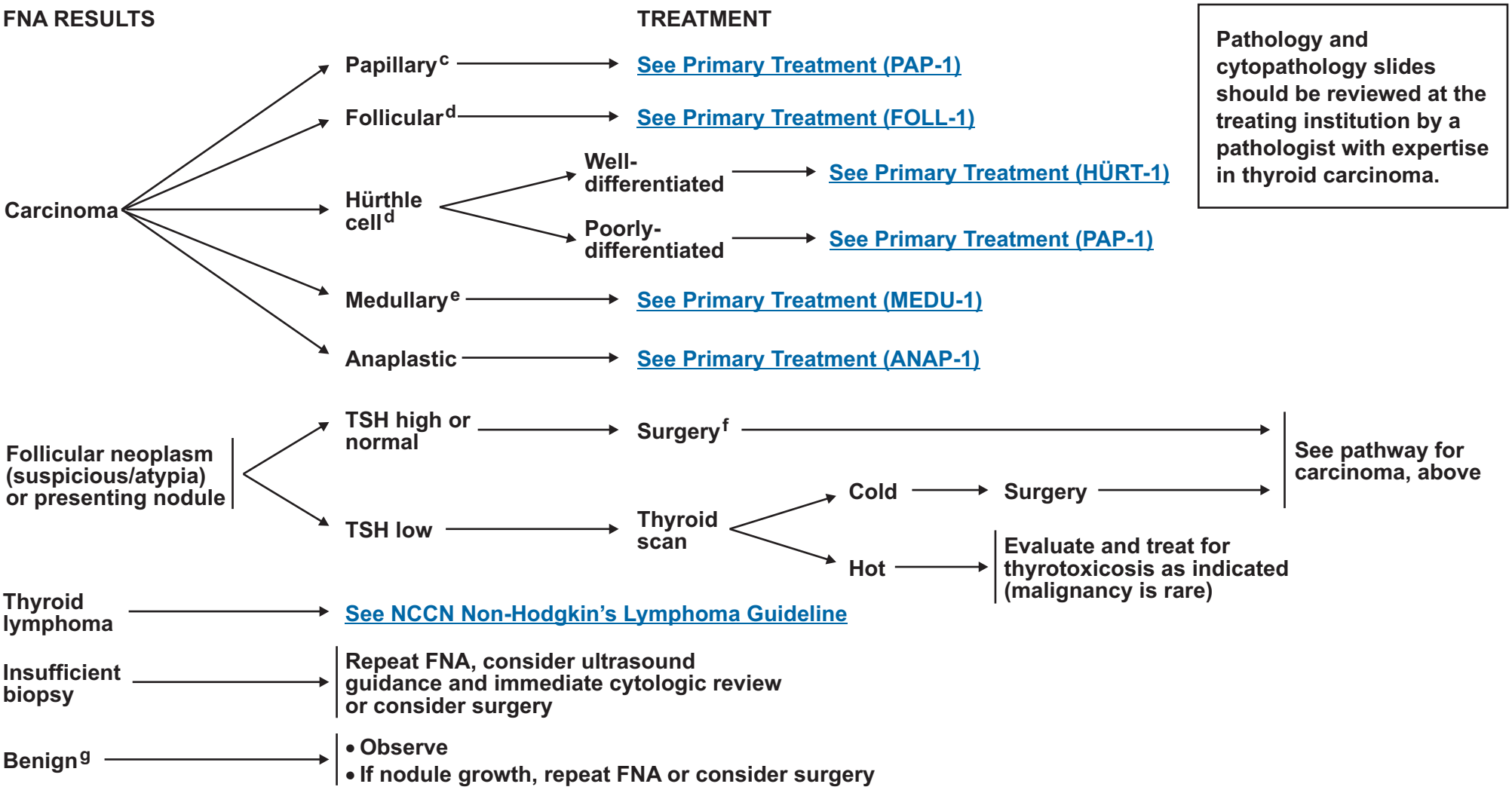
Nodule Evaluation



[c]This includes cytology suspicious for papillary carcinoma.
[d]Rarely diagnosed on FNA.
[e]If suspicious, perform serum calcitonin and CEA.
[f]Consider trial of thyroxine therapy for small, clinically nonsuspicious, follicular neoplasm in a young female patient (category 3).
[g]Macrofollicular, colloid adenoma, Hashimoto's thyroiditis, and Hurthle cells in the absence of neoplasm.

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Papillary Carcinoma

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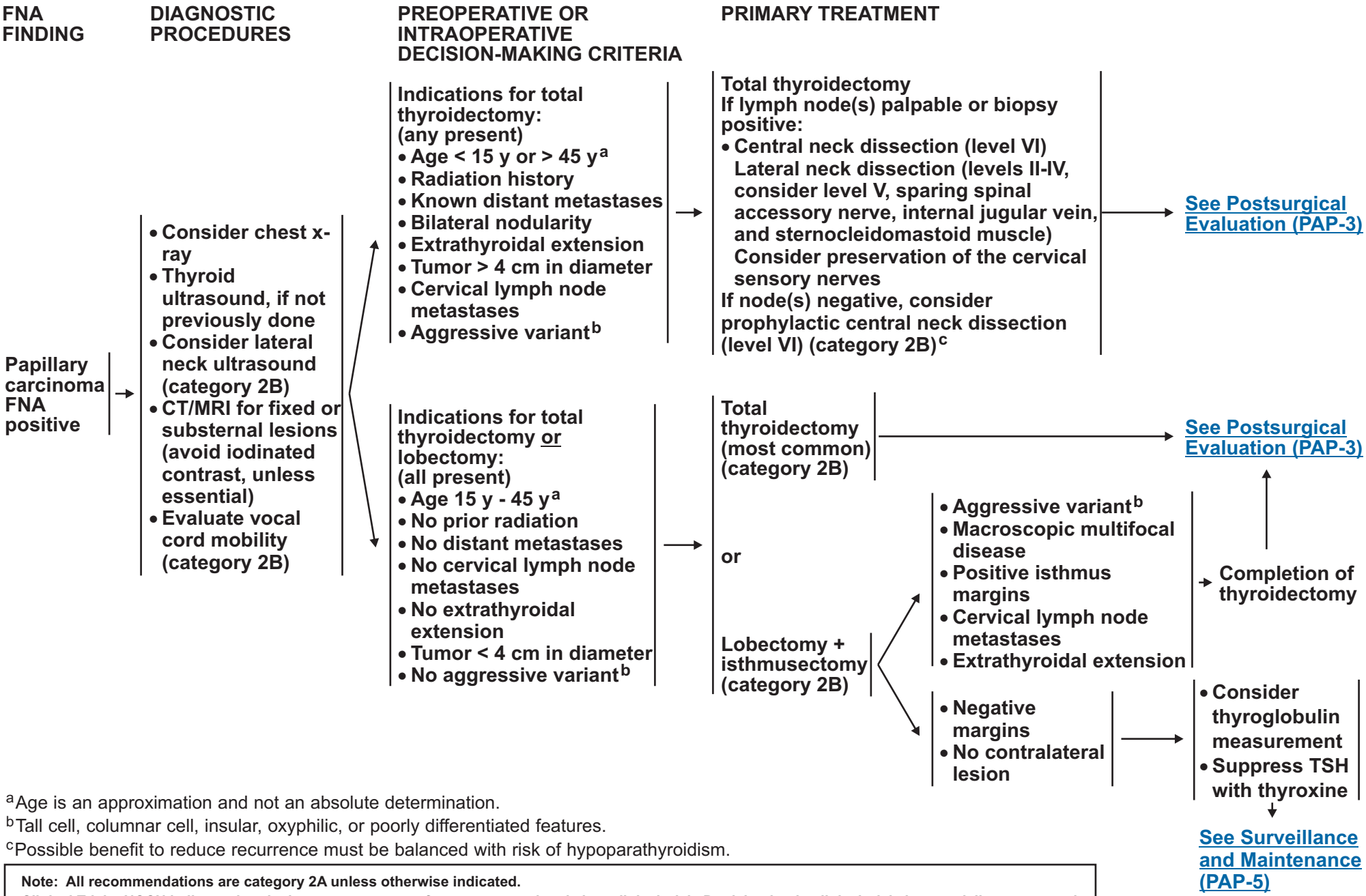

[a] Age is an approximation and not an absolute determination.

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

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

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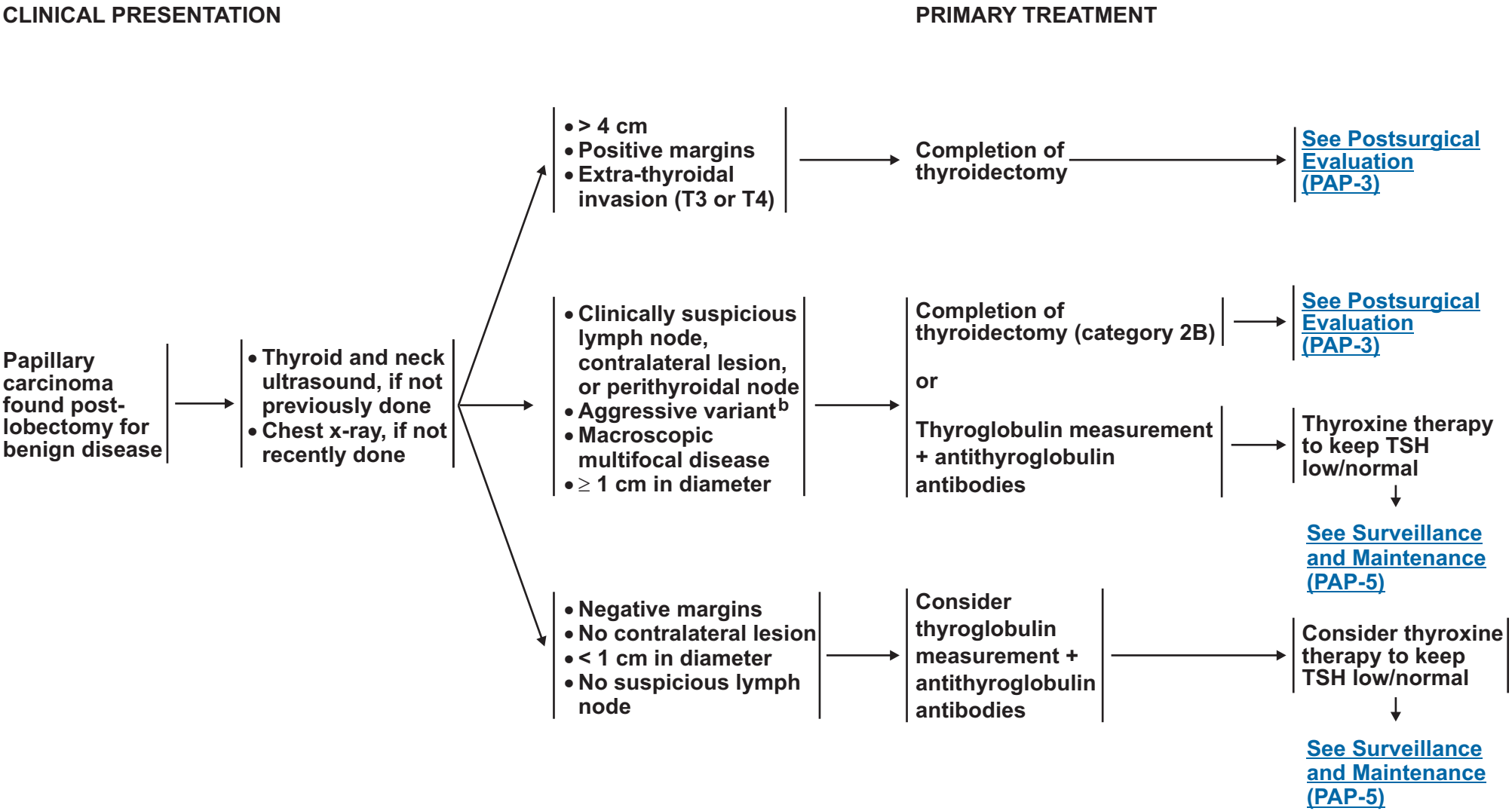

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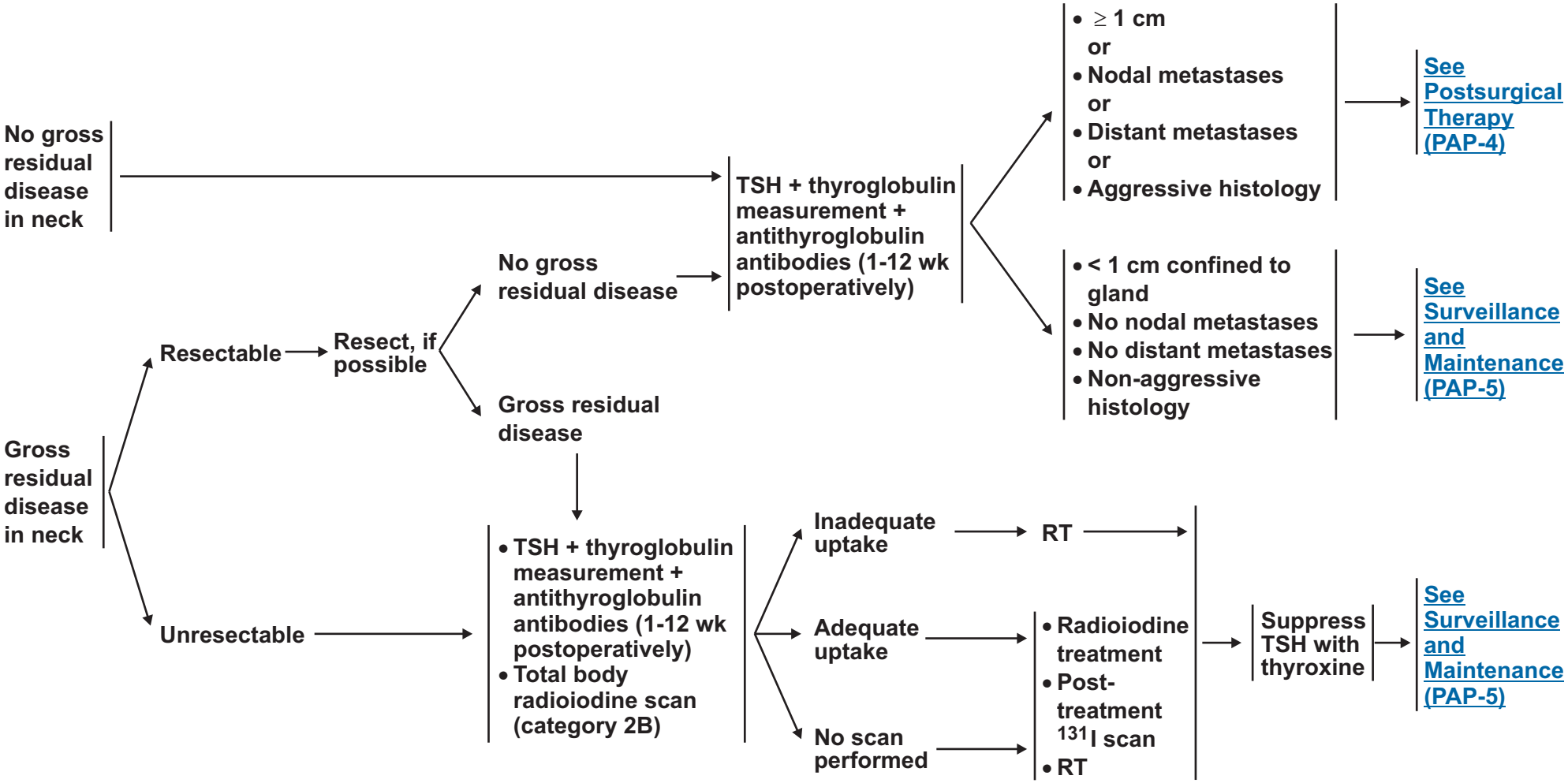
POSTSURGICAL EVALUATION AFTER THYROIDECTOMY



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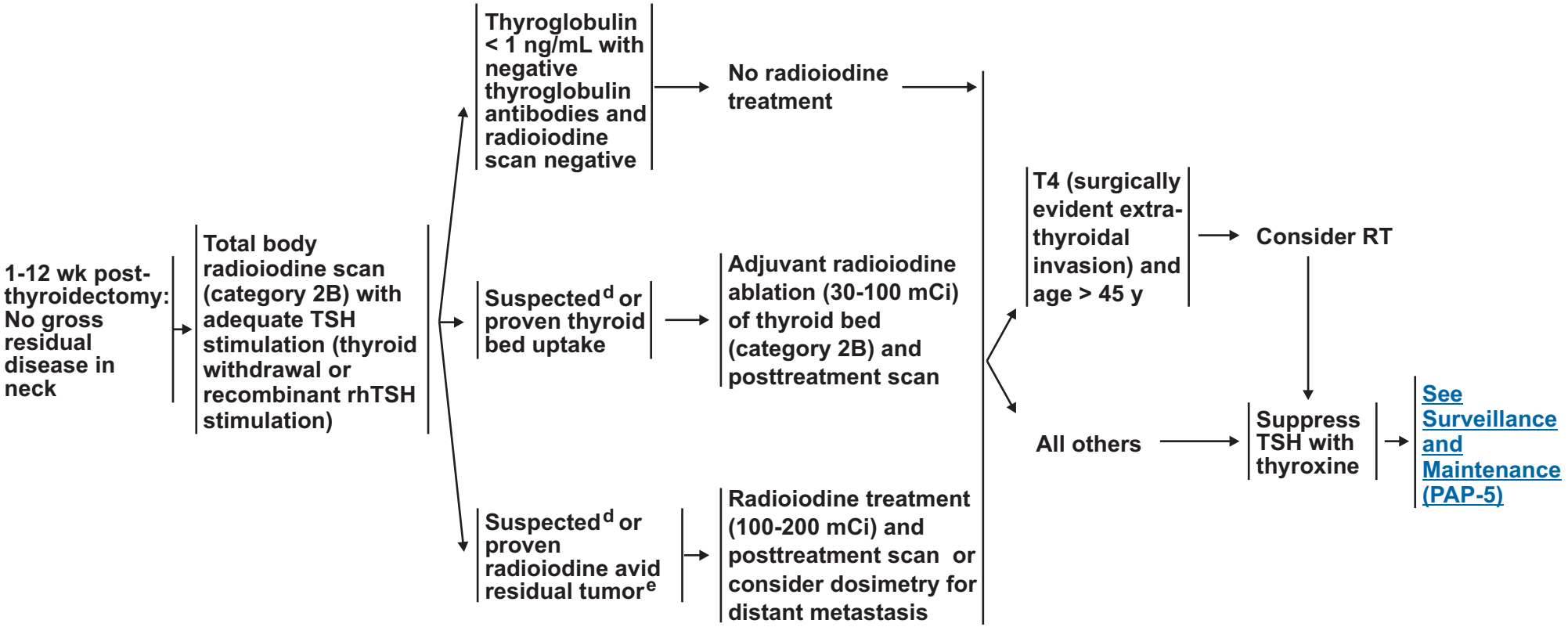
Papillary Carcinoma

POSTSURGICAL THERAPY



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

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

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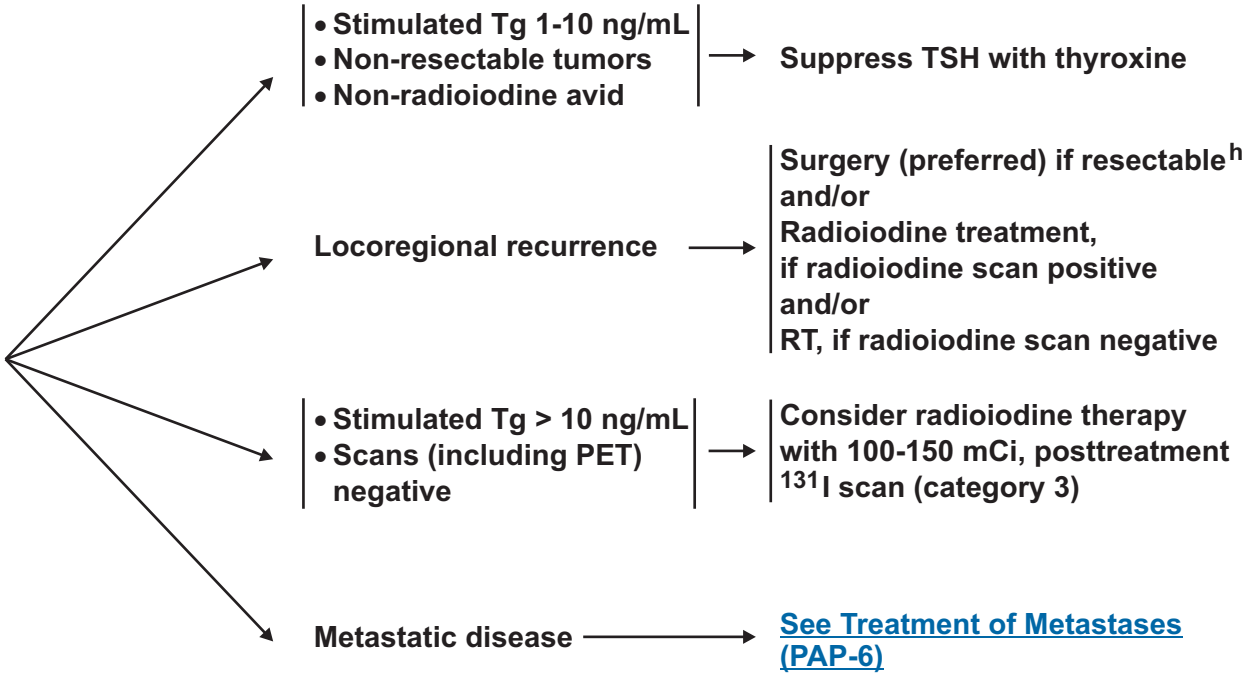
Papillary Carcinoma

SURVEILLANCE AND MAINTENANCE

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

RECURRENT DISEASE



[f]A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[g]If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.
[h]Consider preoperative vocal cord assessment, if central neck recurrence.

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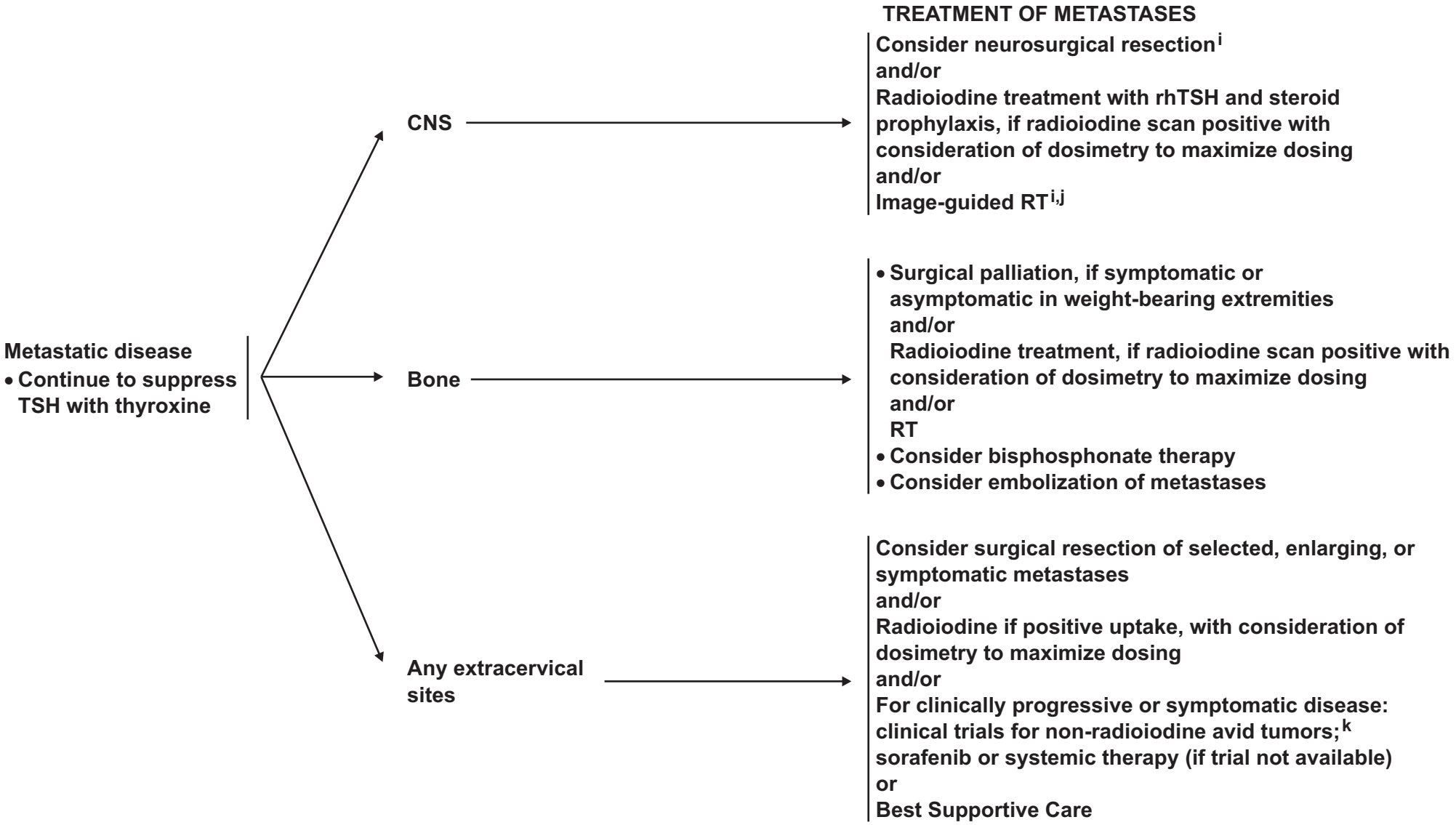
Papillary Carcinoma



[i]For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred.
[j]Does not include whole brain RT.
[k]Cytotoxic chemotherapy has shown to have minimal efficacy. There are agents in clinical trials investigating novel targeted therapies.
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Follicular Carcinoma

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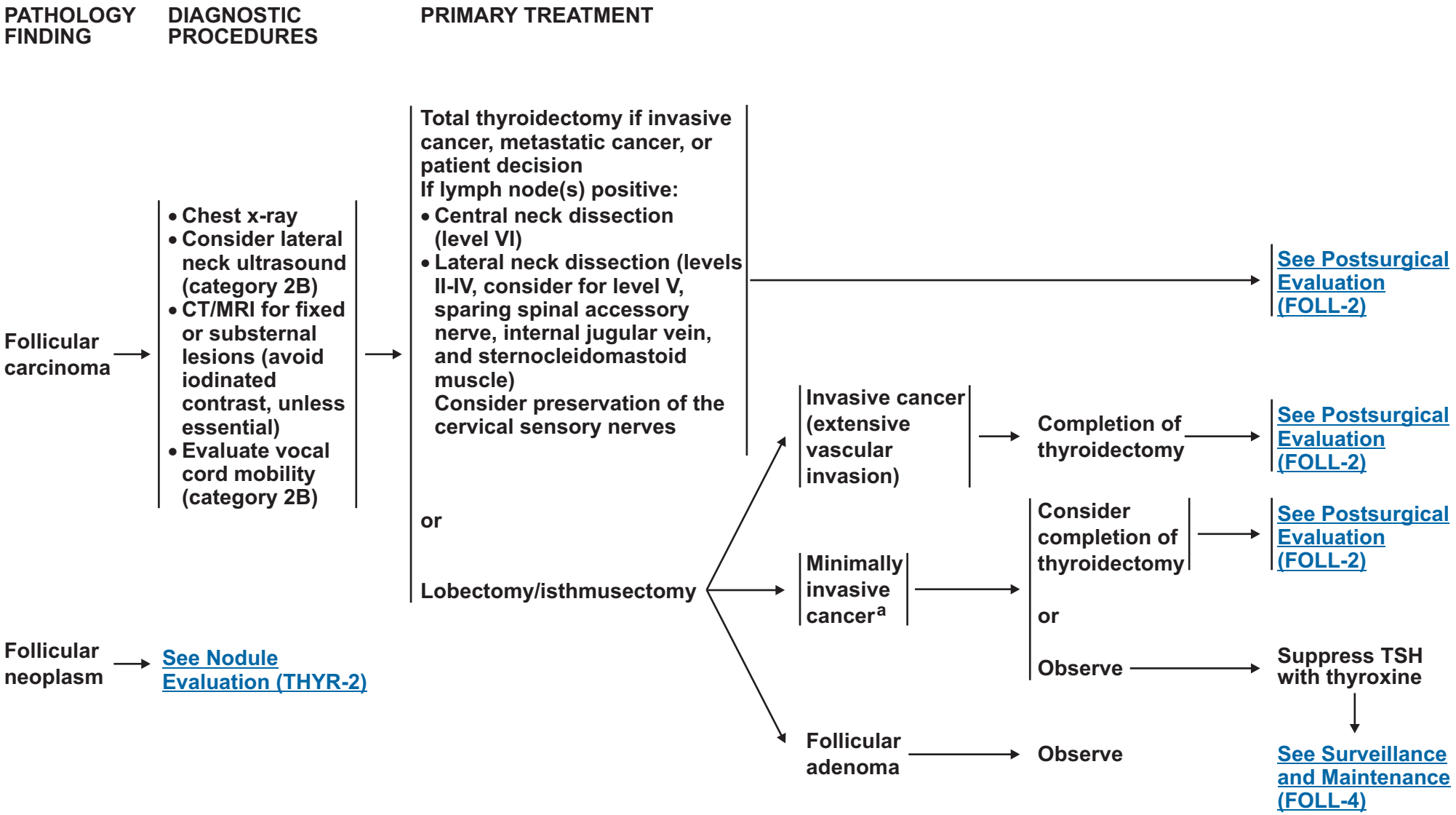

[a]Minimally invasive cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections to demonstrate.

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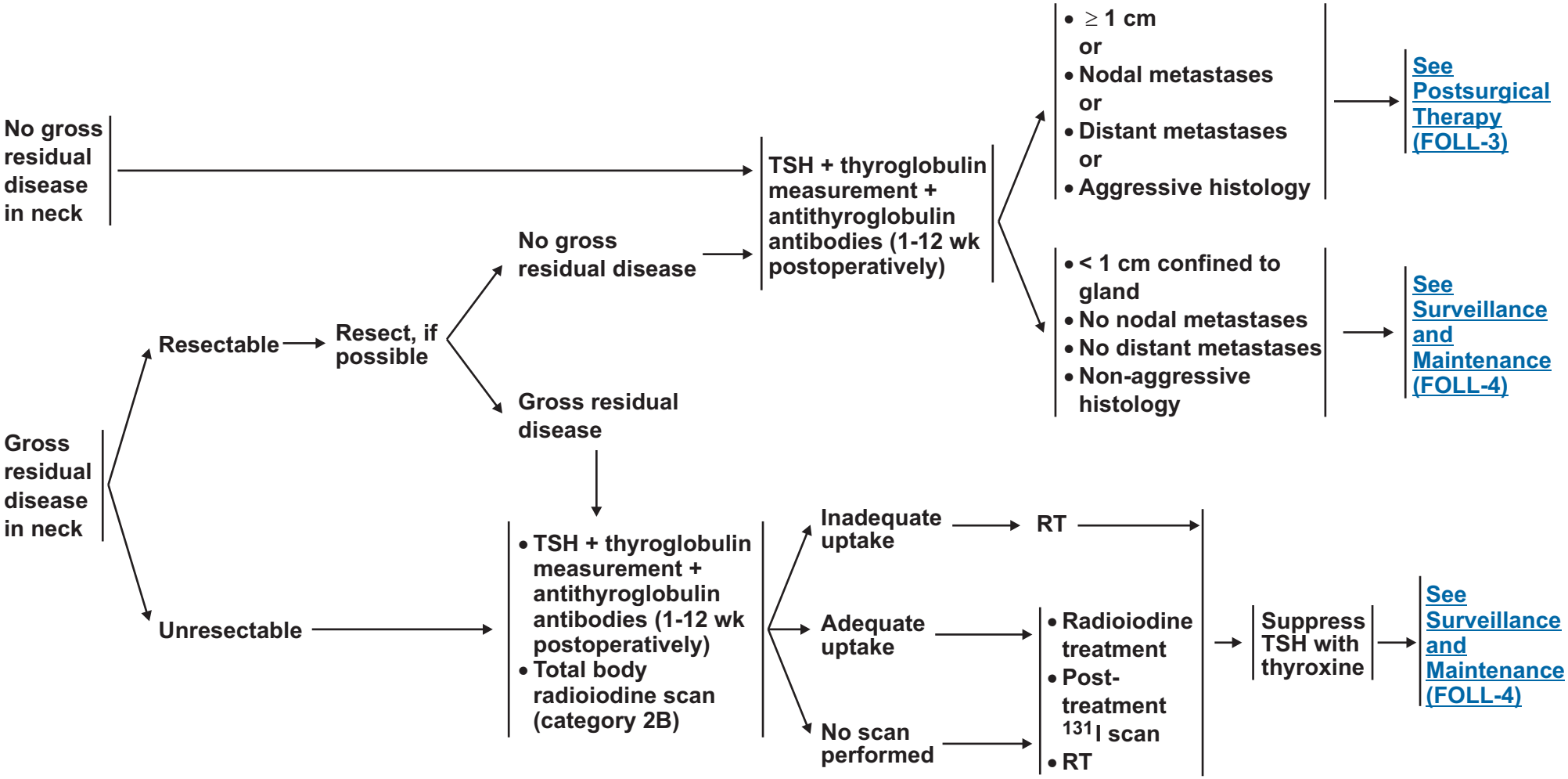
POSTSURGICAL EVALUATION AFTER THYROIDECTOMY



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Follicular Carcinoma

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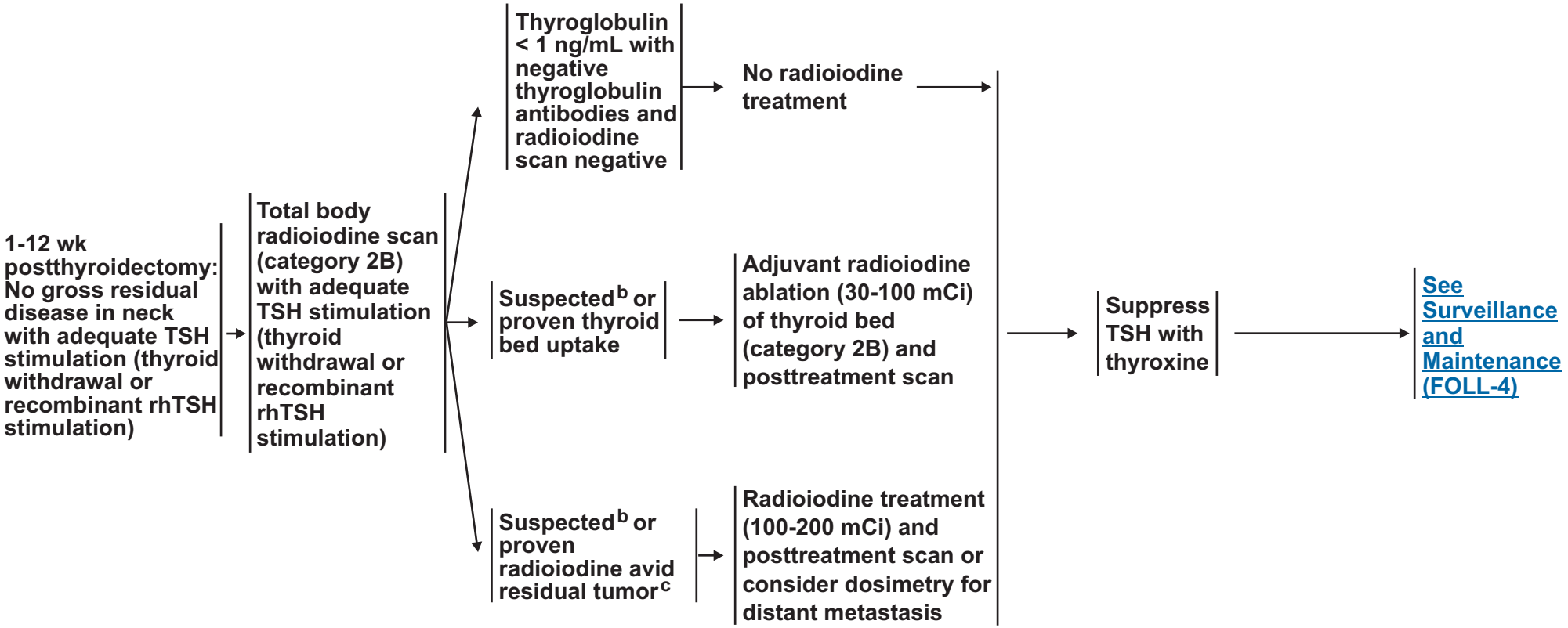

[b] Suspicion based on pathology, postoperative thyroglobulin, and intraoperative findings.

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Follicular Carcinoma

SURVEILLANCE AND MAINTENANCE

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- Periodic neck ultrasound[d]
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- Consider additional nonradioiodine imaging (eg, FDG PET ± CT if Tg ≥ 10 ng/mL), if ^{131}I scans negative and stimulated Tg > 2-5 ng/mL

RECURRENT DISEASE

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

→ Suppress TSH with thyroxine

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

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

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

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

[d]A subgroup of low risk patients may only require an ultrasound if there is a reasonable suspicion for recurrence.
[e]If there is a high likelihood of therapy, thyroid hormone withdrawal suggested; if not, suggest using rhTSH.
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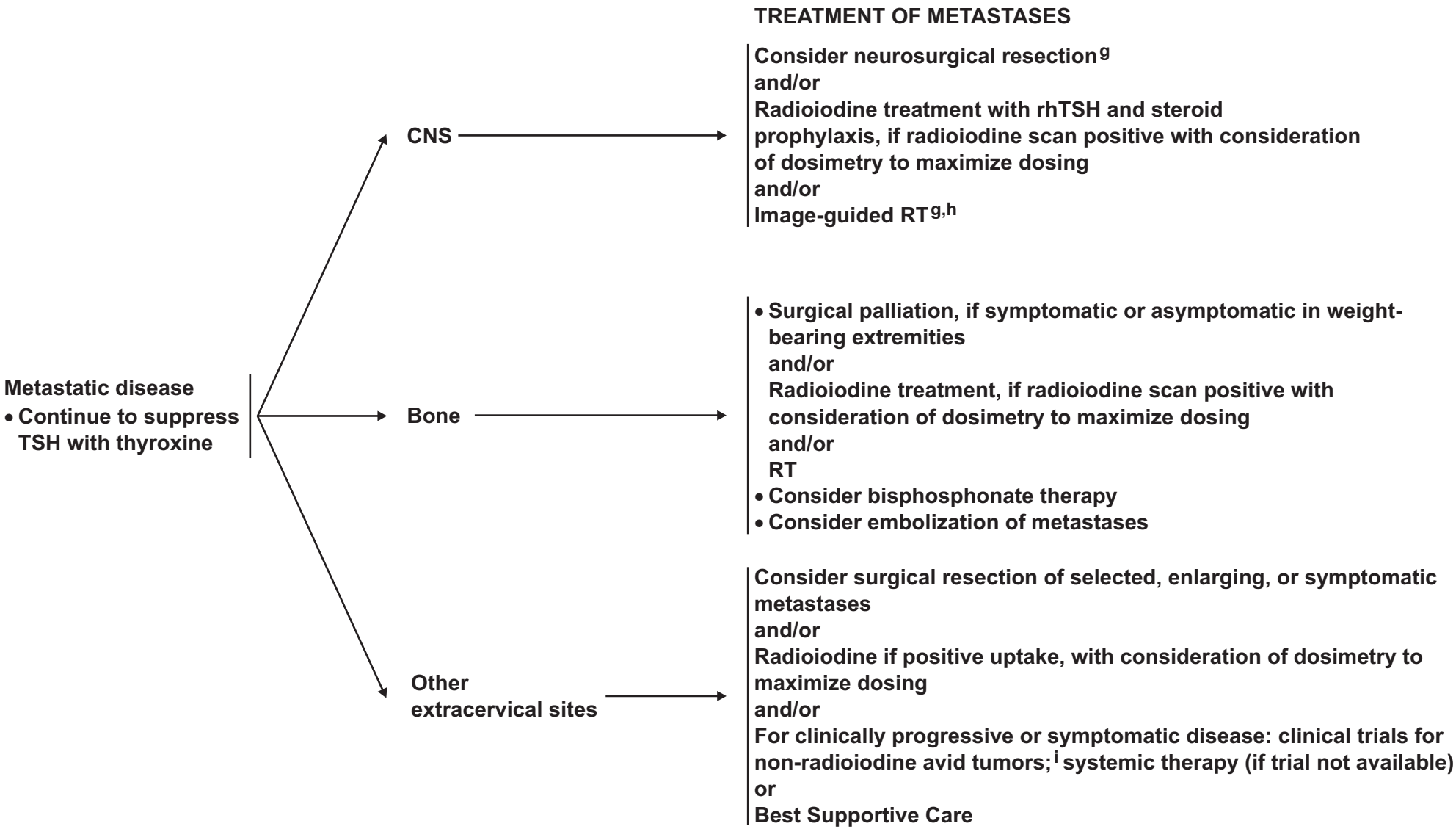

[g] For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred.
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Hürthle Cell Carcinoma

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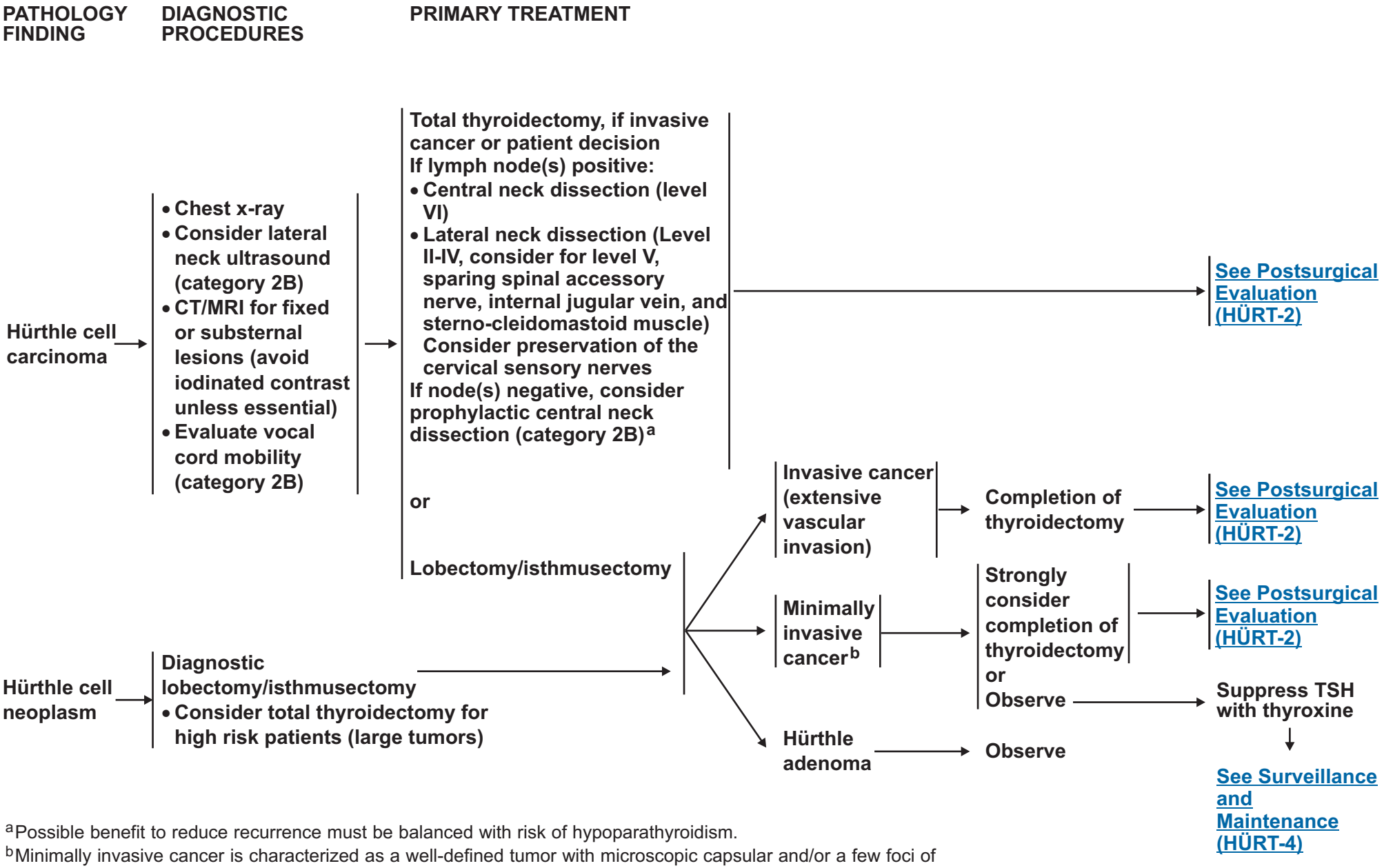

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Hürthle Cell Carcinoma

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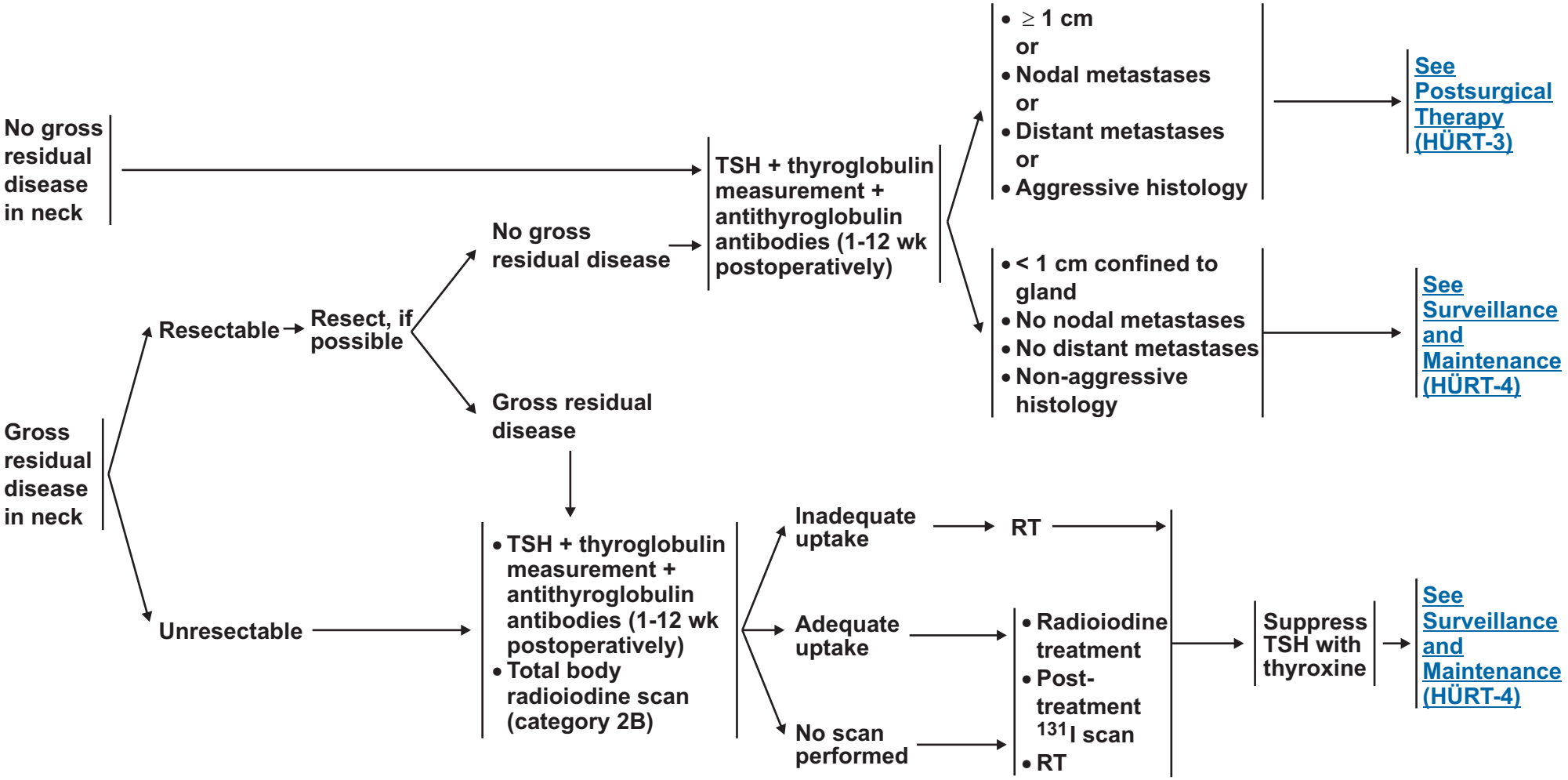

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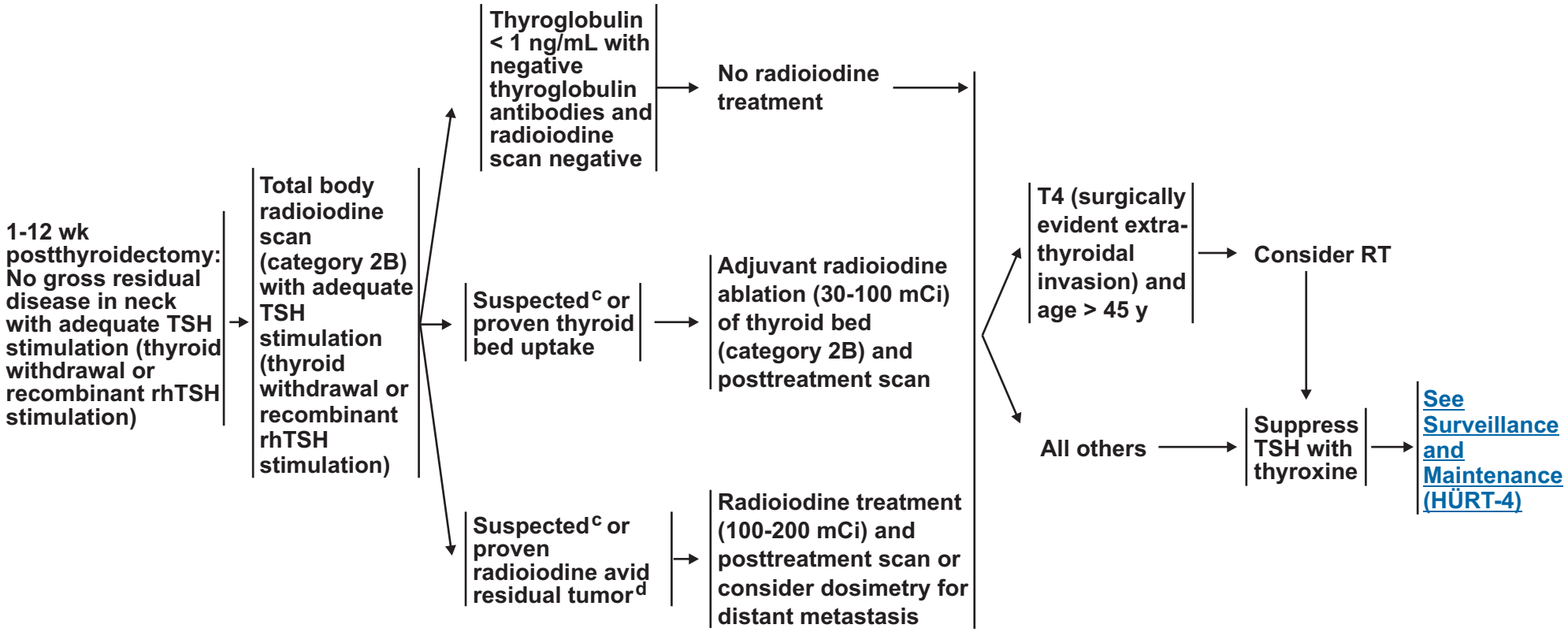
Hürthle Cell Carcinoma

POSTSURGICAL THERAPY



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Hürthle Cell Carcinoma

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RECURRENT DISEASE

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Surgery (preferred) if resectable[g]
and/or
Radioiodine treatment, if radioiodine scan positive
and/or
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Metastatic disease → See Treatment of Metastases (HÜRT-5)

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

TREATMENT OF METASTASES

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

Solitary CNS →
- **Consider neurosurgical resection[h]**
- **and/or**
- **Image-guided RT[h,i]**

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

Other extracervical sites →
- **Consider surgical resection of selected, enlarging, or symptomatic metastases**
- **and/or**
- **Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing**
- **and/or**
- **For clinically progressive or symptomatic disease: clinical trials for non-radioiodine avid tumors;[j]**
- **systemic therapy (if trial not available)**
- **or**
- **Best Supportive Care**

[h] For solitary lesions, either neurosurgical resection or stereotactic radiosurgery preferred.
[i] Does not include whole brain RT
[j] Cytotoxic chemotherapy has shown to have minimal efficacy. There are agents in clinical trials investigating novel targeted therapies.
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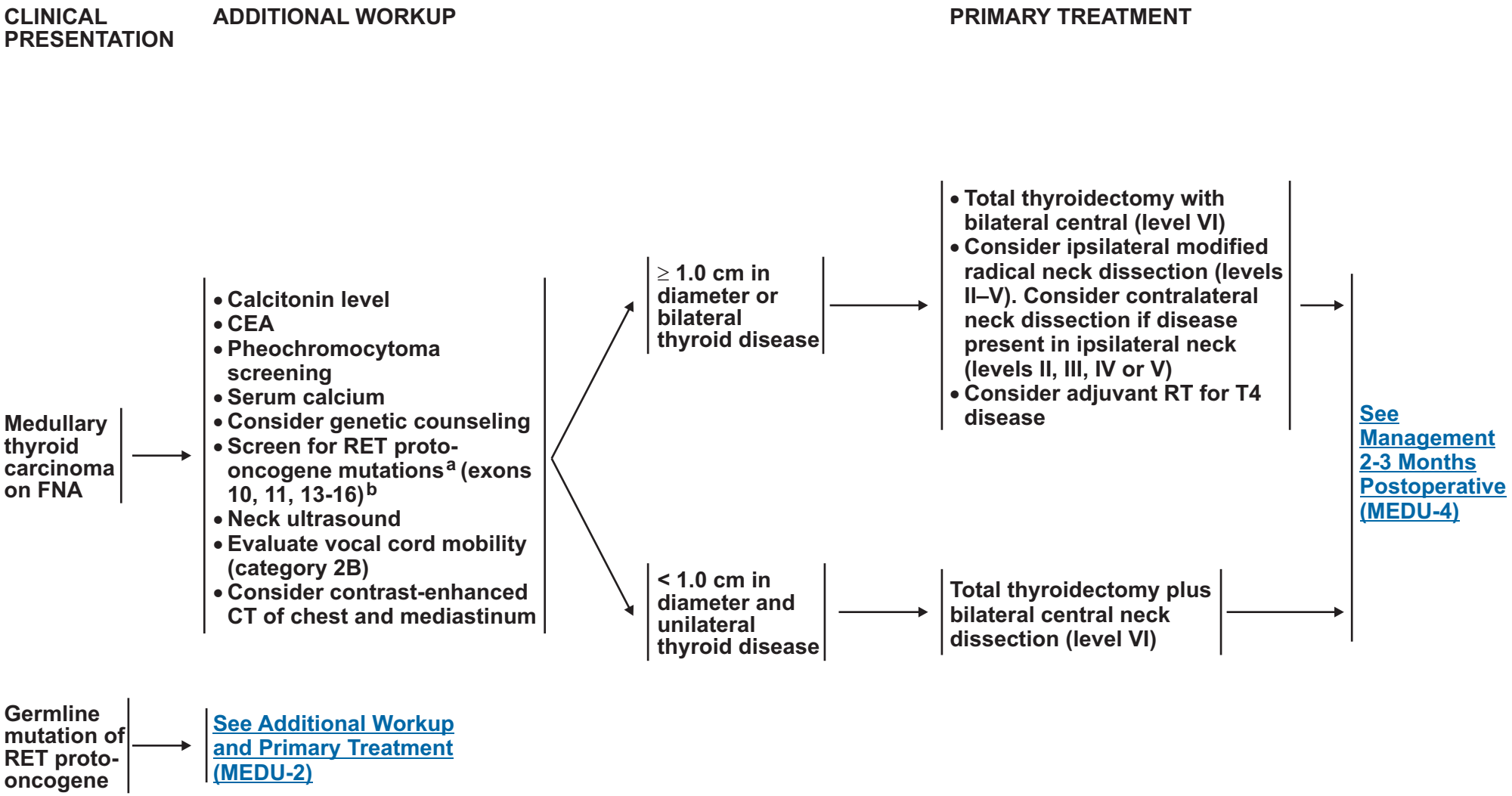
Medullary Carcinoma



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

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

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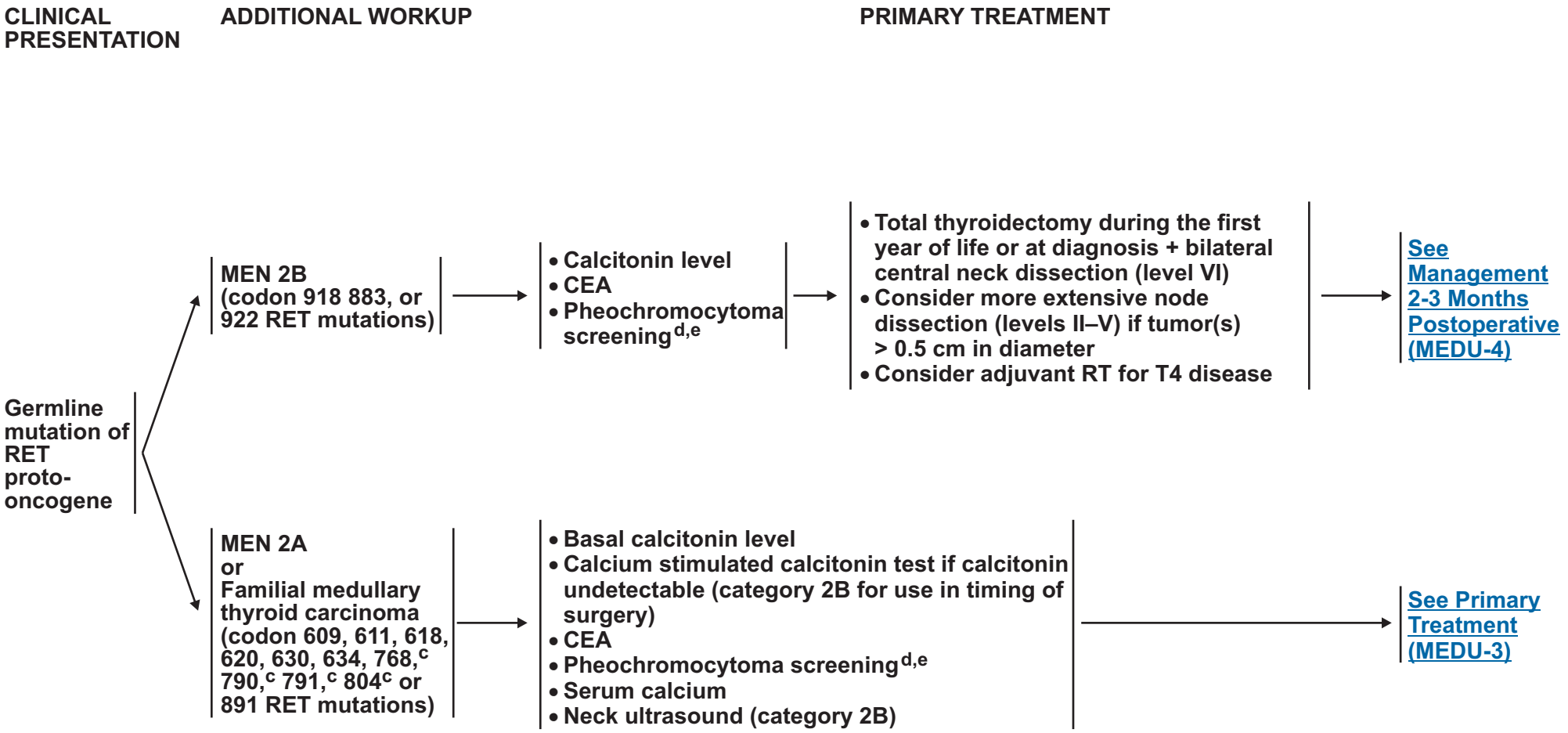
Medullary Carcinoma



[c] Lethality of medullary thyroid carcinoma associated with codon 768, 790, 791, and 804 RET mutations may be lower than with other RET mutations. In patients with these RET mutations, annual provocative (calcium) calcitonin testing may be performed, with total thyroidectomy and central node dissection deferred until tests become abnormal after the age of 5. Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2002;87(6)5658-71.

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

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

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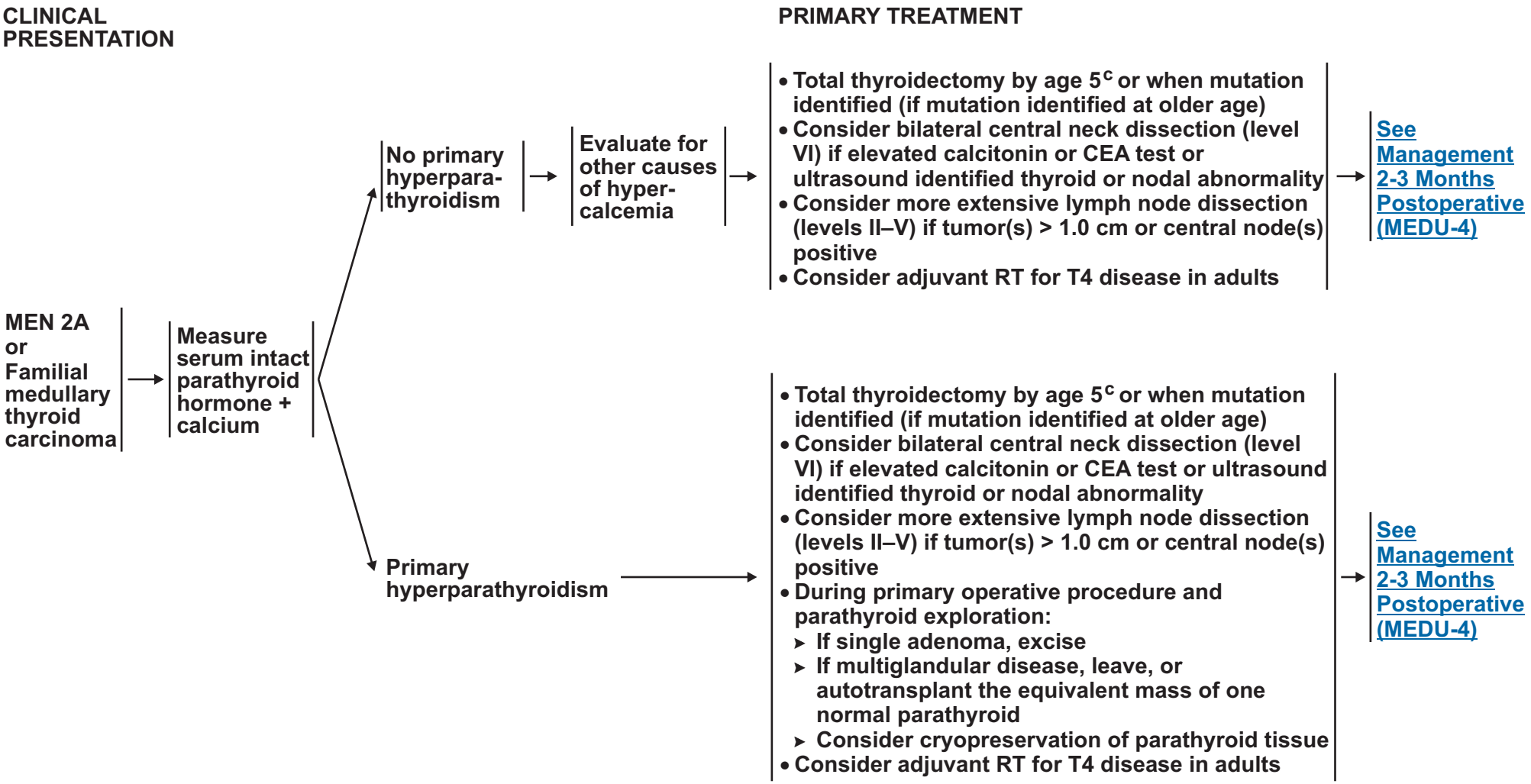
Thyroid Carcinoma TOC
Staging, Discussion, References



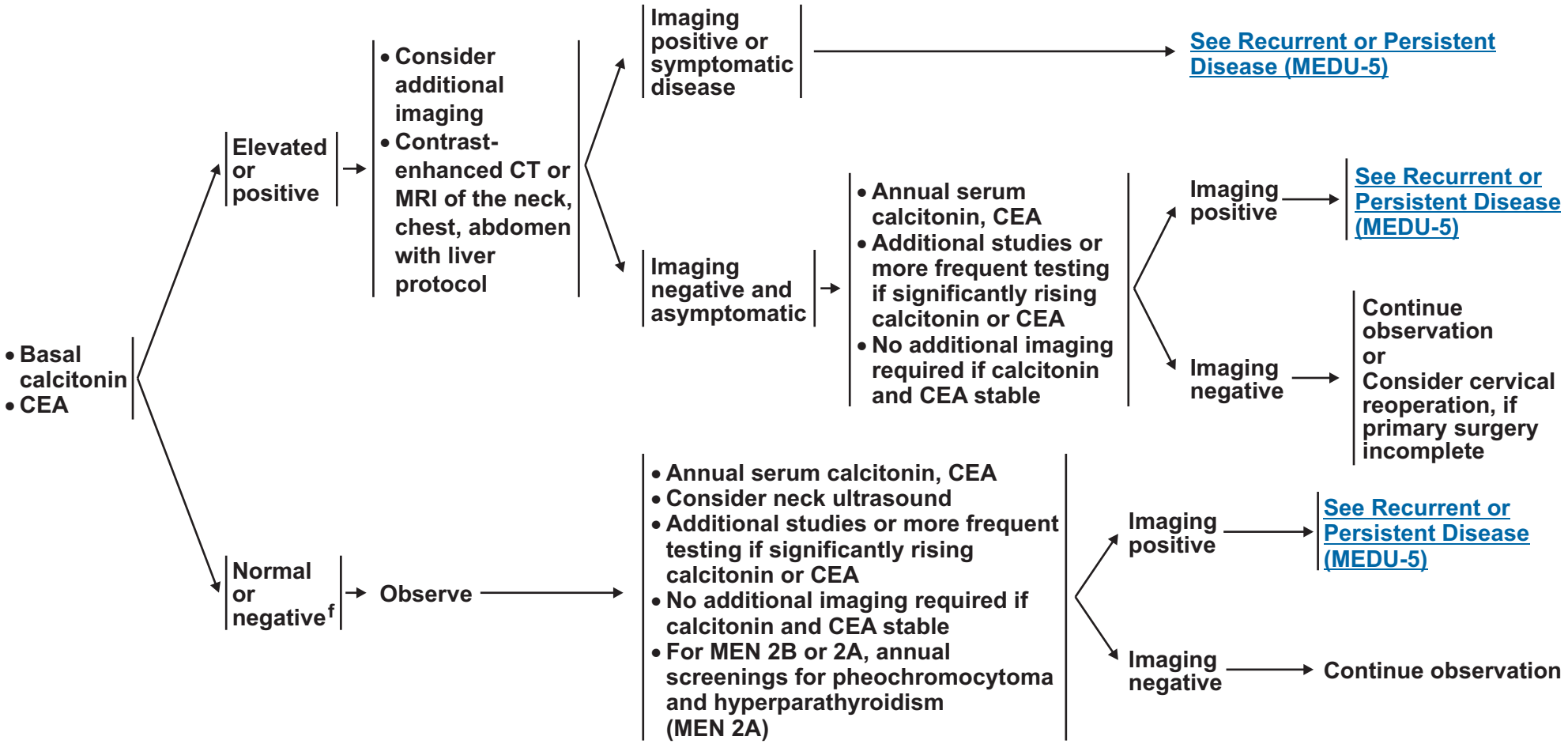
[c]Lethality of medullary thyroid carcinoma associated with codon 768, 790, 791, and 804 RET mutations may be lower than with other RET mutations. In patients with these RET mutations, annual provocative (calcium) calcitonin testing may be performed, with total thyroidectomy and central node dissection deferred until tests become abnormal after the age of 5. Brandi ML, Gagel RF, Angeli A, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2002;87(6)5658-71.

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

Medullary Carcinoma

MANAGEMENT
2-3 MONTHS
POSTOPERATIVE

SURVEILLANCE



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

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

RECURRENT OR PERSISTENT DISEASE

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

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

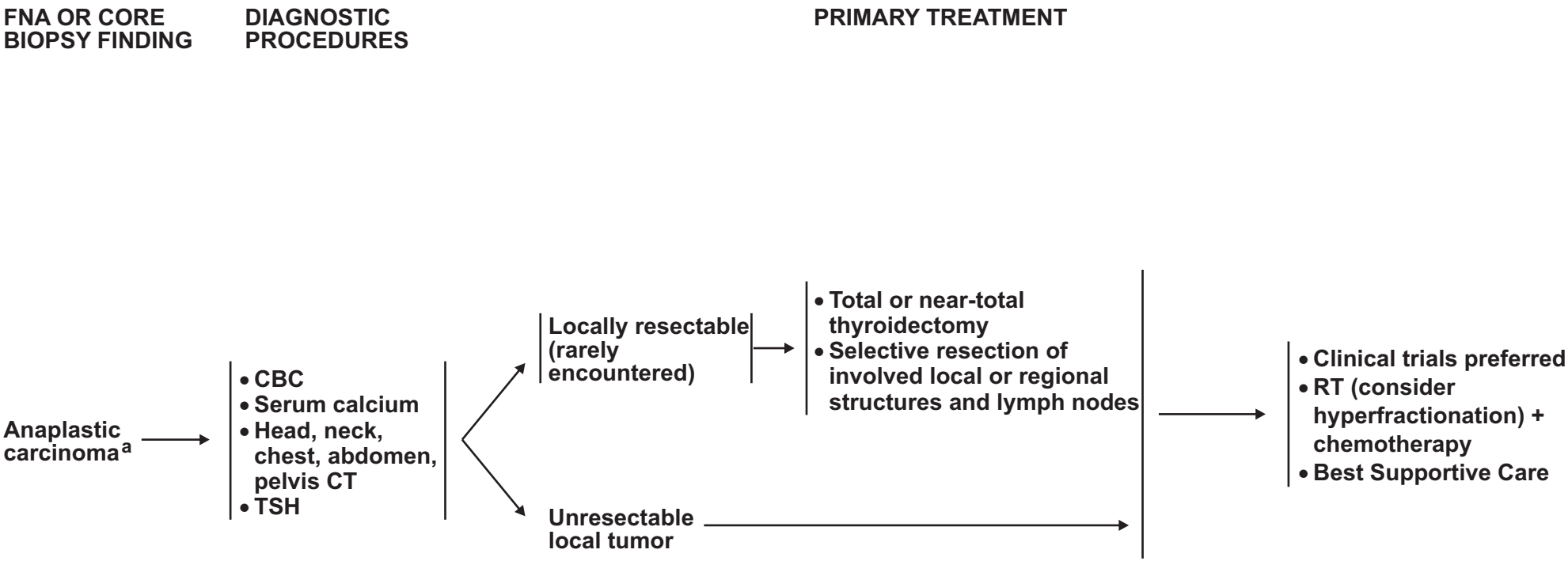
Asymptomatic, distant metastases →
- Observe
  or
  Consider resection, if possible, or ablation (eg, RFA, embolization or other regional therapy) especially if progressive disease

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

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

Anaplastic Carcinoma

Guidelines Index
Thyroid Carcinoma TOC
Staging, Discussion, References



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

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

Staging (2002 AJCC 6th Edition)

Table 1

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

Primary Tumor (T)

Note: All categories may be subdivided: (A) solitary tumor, (b) multifocal tumor (the largest determines the classification).

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

All anaplastic carcinomas are considered T4 tumors.

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

Regional Lymph Nodes (N)

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

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

Distant Metastasis (M)

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

Stage grouping:

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

Papillary or Follicular
Under 45 Years

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

Papillary or Follicular
45 Years and Older

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

Medullary Carcinoma

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

Anaplastic Carcinoma
All anaplastic carcinomas are considered Stage IV

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

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Histopathologic Type

There are four major histopathologic types:

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Epidemiology

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

By contrast, thyroid carcinoma is uncommon. For the U.S. population, the lifetime risk of being diagnosed with thyroid carcinoma is less than 1% (0.84% for women and 0.30% for men).[5] Approximately 37,340 new cases of thyroid carcinoma will be diagnosed in the United States in the year 2008.[6] As with thyroid nodules, this cancer occurs 2 to 3 times more often in women than in men. With the incidence increasing by 6.2% per year, thyroid cancer is currently the eighth most common malignancy diagnosed in women. Among persons aged 15 to 24 years, thyroid cancer accounts for 7.5% to 10% of all diagnosed malignancies.[7] The disease is also diagnosed more often in white North Americans than in African Americans. Although thyroid carcinoma can occur at any age, the peak incidence is around age 45 to 49 years in women and 65 to 69 years in men for the period 2000 to 2004.[5]

There are 3 main histologic types of thyroid cancer: differentiated (including papillary, follicular, and Hürthle), medullary, and anaplastic. Information from the National Cancer Data Base (NCDB) indicates that of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, 80% had papillary carcinoma, 11% had follicular carcinoma, 3% had Hürthle cell carcinoma, 4% had medullary carcinoma, and 2% had anaplastic thyroid carcinoma.[8] In 2008, approximately 1590 cancer deaths will occur among persons living with thyroid carcinoma in the United States.[6] Thyroid carcinoma occurs more often in women; however, mortality rates are higher for men, probably because men are usually older at the time of diagnosis.[5,9]

The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004, but mortality rates decreased more than 44%.[5] From 1975 to 2004, thyroid cancer rates in the United States doubled. Because overall mortality has remained stable since 1975, the increasing incidence probably partially reflects earlier detection of subclinical disease (ie, small papillary cancers), although even microcarcinomas can metastasize regionally, thereby increasing eventual recurrence risk.[10,11] It is also notable that the stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly

with the declining rates being observed with other solid tumors in adults.[6]

The Challenge of Managing Differentiated Thyroid Carcinoma

Managing differentiated (ie, papillary, follicular, and Hürthle) thyroid carcinoma can be a challenge, because no prospective randomized trials of treatment have been done. Results from ongoing randomized trials will not be available for many years, given the typically prolonged course and relative infrequency of these tumors. Most of the information about treatment comes from studies of large patient cohorts in which therapy has not been randomly assigned. This accounts for much of the disagreement about managing differentiated carcinoma. Nonetheless, most patients can be cured of this disease when properly treated by experienced physicians and surgeons.[12] The treatment of choice is surgery, whenever possible, followed in many patients by radioiodine (^{131}I) and thyroxine therapy. 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 carcinogenic action of ionizing radiation. A child's thyroid gland has one of the highest risks of developing cancer of any organ. In fact, the thyroid gland is the only organ linked to risk at about 0.10 Gy by convincing evidence.[3] The risk of radiation-induced thyroid carcinoma is greater in females, certain Jewish populations, and patients with a family history of thyroid carcinoma.[13] This suggests that genetic factors are also important in its development. Beginning within 5 years of irradiation, new nodules develop at a rate of about 2% annually, reaching a peak incidence within 30 years of irradiation but remaining high at 40 years.[3,4]

Previously, most studies showed that ^{131}I is less effective than external gamma radiation in inducing thyroid carcinoma.[14] However, most of the studies that came to this conclusion involved adults, in whom the risk of developing thyroid carcinoma after exposure to ^{131}I appears to be small or nonexistent.[15] After the Chernobyl nuclear reactor accident in 1986, many children developed papillary thyroid carcinoma after being exposed to radioiodine fallout. It became evident that ^{131}I and other short-lived radioiodines were potent thyroid carcinogens in children, particularly those who were younger than 10 years when they were exposed.[16] Although radiation-induced papillary thyroid cancer tends to appear more aggressive histologically and to have high recurrence rates, the prognosis for survival is not clearly different from that of spontaneously occurring tumors.[17,18]

Differentiated Thyroid Carcinoma

Clinical Presentation and Diagnosis

Differentiated (ie, papillary, follicular, or Hürthle) thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. However, evaluating all nodules for malignancy is difficult, because benign nodules are so prevalent and thyroid carcinoma, by contrast, is so uncommon.[1] Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their diagnosis. About 50% of the malignant nodules are discovered during a routine physical examination, by serendipity on imaging studies, or during surgery for benign disease. The other 50% are usually first noticed by the patient, usually as an asymptomatic nodule.[1] 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.[9]

Factors Affecting Risk of Malignancy

Nodule size has a bearing on the risk of malignancy and the clinical evaluation. Thyroid nodules smaller than 1 cm occur with such

frequency in the asymptomatic general population that they are found, in many cases, by serendipity when performing imaging studies for other head or neck problems. Often termed "incidentalomas," nodules smaller than 1 cm are almost invariably clinically benign lesions and usually do not require biopsy.[1,2,19] In selected cases, it may be reasonable to follow these nodules with serial ultrasounds. By contrast, nodules more than 4 cm in diameter are more suggestive and pose a somewhat higher risk of malignancy. Fine-needle aspiration (FNA) is the procedure of choice for evaluating suspicious thyroid nodules.[20] The Society of Radiologists in Ultrasound wrote a consensus statement about management of thyroid nodules identified at thyroid ultrasonography. Their recommendations describe which nodules should undergo FNA and which should not based on nodule size and ultrasound characteristics, and on clinical features that might predict risk of morbidity from an undiagnosed malignancy.[21] Suspicious criteria by 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 THYR-1).[22] For example, the likelihood that a nodule is malignant increases about 7-fold if it is very firm, fixed to adjacent structures, associated with enlarged regional lymph nodes, causes vocal cord paralysis, or is rapidly growing or if symptoms of invasion into neck structures are present.[22,23] If 2 or more of these features are present, the likelihood of thyroid cancer is virtually assured.[23]

A patient's age and gender also affect the probability of malignancy. The risk of malignancy is higher in patients younger than 15 years and older than 60 years. In particular, a man older than 60 years with a thyroid nodule has about 4 times the risk of having thyroid carcinoma than does a middle-aged woman with a thyroid nodule.[24] Other factors that increase the suspicion of malignancy include (1) a history of head and neck irradiation; (2) a family history of thyroid carcinoma; (3) the presence of familial syndromes associated with thyroid carcinoma (see "Familial Syndromes"), such as Gardner's syndrome, familial adenomatous polyposis, Carney complex, Cowden's syndrome, and multiple endocrine neoplasia (MEN) types 2A or 2B; (4) evidence of other diseases seen with 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 (5) the presence of suspicious findings detected by imaging such as focal FDG (18-fluorodeoxyglucose) uptake on positron emission tomography (PET), or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.[25]

Initial Workup

Fine-needle aspiration 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 done.[1] Ideally, the serum thyrotropin (thyroid-stimulating hormone [TSH]) results should be known before FNA is performed. This is often impractical, however, and FNA may be done during the initial office visit.

Some clinicians, especially in Europe,[26] recommend obtaining serum calcitonin levels from all patients with thyroid nodules. However, there is controversy surrounding 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. To date, this practice has not been recommended by the American Thyroid Association.[27] A recent study showed that calcitonin screening may be cost effective in the United States.[28] However, false-positive calcitonin readings that can result from minimal calcitonin elevations can only be ruled out with pentagastrin testing, and

pentagastrin is not available in the United States. Ultrasound of the thyroid and neck including central and lateral neck compartments is also recommended (category 2B).[29]

Cytologic examination of an FNA specimen, with sufficient cells recovered to assign a diagnosis, is typically categorized as (1) carcinoma; (2) suspicious for malignancy, including follicular neoplasms; (3) thyroid lymphoma; and (4) benign (such as macrofollicular, colloid adenoma, Hashimoto's thyroiditis, Hürthle cells in the absence of neoplasm). Both the National Cancer Institute (NCI) (http://thyroidfna.cancer.gov/pages/conclusions/) and the Papanicolaou Society of Cytopathology have guidelines for thyroid FNA (http://www.papsociety.org/guidelines.html).

Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in the diagnosis of thyroid disorders. Although FNA is a very sensitive test—particularly for papillary—false-negative results are sometimes obtained; therefore, a reassuring FNA should not override concerns in the presence of worrisome clinical findings.[30]

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

http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Fcancer%2Fcancer_protocols%2Fprotocols_index.html&_state=maximized&_pageLabel=cntvwr

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 the diagnostic criterion for these malignancies requires demonstration of vascular or capsular invasion. Thus, follicular and Hürthle cell carcinomas are rarely diagnosed on FNA. Nodules that yield an abundance of follicular cells with little or no colloid are nearly impossible to categorize as benign or malignant on the basis of FNA. Surgical biopsy is advisable, because approximately 20% of these lesions are follicular carcinomas.[22] Male gender, older patient age, and larger nodule size may increase the likelihood of a malignant diagnosis at surgery as high as 80%, whereas female gender, younger age, and smaller nodule size may reduce the risk as low as 5%. Repeat FNA will not resolve the diagnostic dilemma. Before thyroidectomy is performed, however, serum TSH level and thyroid ^{123}I or 99m technetium scanning may identify patients with an autonomously functioning or "hot" nodule who often may be spared surgery, because the diagnosis of follicular adenoma is highly likely.[31] Clinically euthyroid patients with a low TSH and a hot nodule on thyroid scan should be evaluated and treated for thyrotoxicosis as indicated even when cytology is suspicious for follicular neoplasm; those with a "cold" nodule should proceed to surgery. Those patients with a high or normal TSH and cytology suspicious for follicular or Hürthle cell neoplasm should undergo open biopsy with thyroidectomy. A trial of

thyroxine therapy may be considered for a small, clinically nonsuspicious, follicular neoplasm in a young female patient, although the panel disagreed about this recommendation (category 3). If the patient receives thyroxine therapy, re-aspiration or surgery should be performed if the lesion grows.

Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of growth.[22] The use of thyroid hormone to suppress benign thyroid nodules is controversial with modest clinical impact at best, and a perceived cost/benefit ratio that is not compelling.[32,33]

An FNA that yields insufficient cellular material for diagnosis should be repeated, because approximately 50% of subsequent specimens are adequate to assign a diagnosis.[22] In patients with serial nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules.[34]

When a diagnosis of thyroid carcinoma is promptly established using FNA, the tumor is often confined to the thyroid or has metastasized only to regional nodes, thus providing ample opportunity for cure. However, as many as 5% of patients with papillary carcinoma and up to 10% of those patients with follicular or Hürthle cell carcinoma have tumors that aggressively invade structures in the neck or have produced distant metastases. Such cancers are difficult to cure.

Prognosis and Recurrence of Differentiated Thyroid Carcinoma

In the NCDB study, the 10-year relative survival rates for patients with papillary, follicular, and Hürthle cell carcinomas were 93%, 85%, and 76%, respectively.[8] Although anaplastic thyroid carcinoma is almost uniformly lethal, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases.

Depending on initial therapy and other prognostic variables, about 30% of patients with differentiated thyroid carcinoma have tumor recurrences during several decades; 66% of these recurrences occur within the first decade after initial therapy.[9] Although not usually fatal, a recurrence in the neck is serious and must be regarded as the first sign of a potentially lethal outcome.[35,36] 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.[9] 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.[9]

Age, Stage, and Sex at Diagnosis

Although many factors influence the outcome for patients with papillary and follicular thyroid carcinomas, the 2 most important and consistently demonstrable are patient age at the time of initial therapy and tumor stage.[9,37-39] Age is the most important prognostic variable for thyroid cancer mortality. However, thyroid cancer is more aggressive in men. Thyroid carcinoma is more lethal in patients older than 40 years, increasingly so with each subsequent decade of life. The mortality rate increases dramatically after age 60 years (see Figure 1). However, tumor recurrence shows a remarkably different behavior with respect to age. Recurrence frequencies are highest (40%) for those younger than 20 years or older than 60 years; recurrence at other ages ensues in only about 20% of patients.[9,37-40] This disparity between cancer-related mortality and the frequency of tumor recurrence probably accounts for most of the profound disparity of opinion among clinicians concerning optimal treatment for patients with differentiated thyroid cancer. How clinicians assess the importance of tumor recurrence (as opposed to cancer-specific survival) accounts for much of the debate surrounding the influence of age on the treatment plan for children and young adults.

Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good.[41,42] One study found, however, that although the prognosis of children with thyroid carcinoma is favorable for long-term survival (90% at 20 years), the standardized mortality ratio was 8-fold higher than predicted.[43] Some authors believe that young age in a patient imparts such a favorable influence on survival that it overshadows the behavior expected from the characteristics of the tumor. Therefore, they classify most thyroid tumors as low-risk tumors that may be treated with lobectomy alone,[44-46] although most physicians treating the disease believe that tumor stage and its histologic features should be as significant as the patient's age in determining management.[9,41,47,48]

Prognosis is less favorable in men than in women, but the difference is usually small.[9,46] One study found that gender was an independent prognostic variable for survival and that the risk of death from cancer was about twice as high in men as in women.[9] Because of this risk factor, men with thyroid carcinoma, especially those who are older than 40 years, may be regarded with special concern.[49]

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.[50] One study found that 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.[51] Other familial syndromes associated with papillary thyroid carcinoma are Gardner's syndrome, familial adenomatous polyposis,[52] Carney complex (multiple neoplasia and lentiginosis syndrome which affects endocrine glands),[53] and Cowden's syndrome (multiple hamartomas).[54] The prognosis for all of these syndromes is not different from the prognosis of spontaneously occurring papillary thyroid carcinoma.

Tumor Variables Affecting Prognosis

Some tumor features have a profound influence on prognosis.[40,55-57] Perhaps the most important features are tumor histology, primary tumor size, local invasion, necrosis, vascular invasion, BRAF mutation status, and metastases. A somatic RET oncogene mutation in sporadic medullary thyroid cancer confers an adverse prognosis.[58]

Histology

Although survival rates with typical papillary carcinoma are quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors.[1] A well-defined tumor capsule, which is found in about 10% of papillary thyroid carcinomas, is a particularly favorable prognostic indicator. A 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.[59] Follicular-variant papillary carcinoma, which is recognized by its follicular architecture and typical papillary cytology, does not appear to have a worse prognosis than the pure papillary lesions.[40,59,60]

Follicular carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It usually has a microfollicular histologic pattern. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.[61] Many follicular carcinomas are minimally invasive tumors, exhibiting only slight tumor capsular penetration without vascular invasion. They closely resemble follicular adenomas and are less likely to produce distant metastases or to cause death.[62] 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 THYR-2). The diagnosis of cancer may be assigned only after thyroidectomy and indeed only after analysis of the "permanent" histologic sections shows tumor capsule invasion by follicular cells.

Highly invasive follicular carcinomas are much less common; they are sometimes recognized at surgery by their invasion of surrounding tissues and extensive invasion of blood vessels. Up to 80% of these cancers metastasize, causing death in as many as 20% of patients, often within a few years of diagnosis.[40] The poor prognosis is closely related to the patient's older age at the time of diagnosis, advanced tumor stage, and larger tumor size.[9]

The mortality for papillary and follicular carcinomas is similar in patients of comparable age and disease stage. Both cancers have an excellent prognosis if the tumors are confined to the thyroid, are small, and are minimally invasive. Both papillary and follicular carcinomas have far less favorable outcomes if they are highly invasive or develop distant metastases.[9,63] Note that staging for patients with papillary and follicular carcinoma who are older than 45 years has been revised in the 2002 guidelines (6th edition) from the American Joint Commission on Cancer (AJCC) (see Table 1).[64] Many studies (including those discussed in this manuscript) have been based on AJCC-TNM staging from earlier editions, such as the 5th edition[65] and not the 6th edition.[64]

When Hürthle (oncocytic) cells constitute most or all of a malignant tumor's mass, the disease is often classified as Hürthle cell carcinoma, although the World Health Organization classification considers it as a variant of follicular carcinoma.[66] Molecular studies suggest, however, that this tumor may be more similar to papillary than follicular carcinomas.[67] Benign and malignant Hürthle tumors usually cannot be discriminated by FNA or frozen section examination, although large (>4 cm) tumors are more likely to be malignant than smaller ones.[68] Hürthle cell carcinomas may be aggressive, especially when vascular invasion or large tumors occur in older patients.[69,70] Some believe these cancers are not much more aggressive than similarly staged follicular carcinomas without Hürthle cells.[71] In the NCDB report, the 10-year relative survival rates were 85% for follicular carcinomas and 76% for Hürthle cell carcinoma.[8]

In 2 large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, about twice the frequency of follicular carcinoma metastases.[72,73] Fewer Hürthle cell carcinomas concentrate ^{131}I than do papillary or follicular carcinomas. The University of Texas M.D. Anderson Cancer Center reported that in a series of 100 patients with distant metastases, ^{131}I uptake by pulmonary metastases was seen in more than 50% of the follicular (64%) and papillary (60%) carcinomas but in only 36% of Hürthle cell carcinomas.[74]

Primary Tumor Size

Papillary carcinomas smaller than 1 cm, termed "*microcarcinomas*," are typically found incidentally after surgery for benign thyroid conditions. Their recurrence and cancer-specific mortality rates are near zero.[75,76]

Other small papillary carcinomas become clinically apparent. For example, about 20% of microcarcinomas are multifocal tumors that commonly metastasize to cervical lymph nodes. Some researchers report a 60% rate of nodal metastases from multifocal microcarcinomas,[77] which may be the presenting feature and also may be associated with distant metastases.[76] Otherwise, small (< 1.5 cm) papillary or follicular carcinomas confined to the thyroid almost never cause distant metastases. Furthermore, rates of recurrence after 30 years are one third of those associated with larger tumors; 30-year cancer-specific mortality is 0.4% compared to 7% (P<.001) for tumors 1.5 cm or larger.[9] In fact, the prognosis for papillary and follicular

carcinomas is incrementally poorer as tumors increase in size.[63,78] There is a linear relationship between tumor size and recurrence or cancer-specific mortality for both papillary and follicular carcinomas (see Figure 2).[9]

Local Tumor Invasion

Up to 10% of differentiated thyroid carcinomas invade through the outer border of the gland and grow directly into surrounding tissues, increasing both morbidity and mortality. The local invasion may be microscopic or gross; it can occur with both papillary and follicular carcinomas.[9,79] Recurrence rates are 2 times higher with locally invasive tumors, and as many as 33% of patients with such tumors die of cancer within a decade.[9,80]

Lymph Node Metastases

In one review, nodal metastases were found in 36% of 8029 adults with papillary carcinoma, in 17% of 1540 patients with follicular carcinoma, and in up to 80% of children with papillary carcinoma.[40] An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery.[81] The prognostic importance of regional lymph node metastases is controversial. Some studies find that the presence of regional lymph node metastases has no effect on recurrence or survival.[44-46] Other studies find that nodal metastases are a risk factor for local tumor recurrence and cancer-specific mortality and that nodal metastases correlate with distant metastases, especially if there are bilateral cervical or mediastinal lymph node metastases or if the tumor invades through the lymph node capsule.[9,39,82] In one study, 15% of patients with cervical node metastases died of thyroid carcinoma ($P<.02$), whereas all patients without cervical node metastases survived.[83] Another study of patients with distant metastases from papillary carcinoma reported that 80% had mediastinal node metastases at the time cancer was diagnosed.[84] Still another study found that patients with papillary or follicular carcinoma who had cervical or mediastinal lymph node metastases had a significantly ($P<.01$) higher 30-year cancer-specific mortality (10%) than patients without metastases (6%).[9]

Distant Metastases

Distant metastases are the principal cause of death from papillary and follicular carcinomas. Almost 10% of patients with papillary carcinoma and up to 25% of those with follicular carcinoma develop distant metastases. About 50% of these metastases are present at the time of diagnosis.[40] Distant metastases occur even more often in patients with Hürthle cell cancer (35%) and in those patients diagnosed after age 40 years.[72,74] 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's age, the tumor's metastatic site, ability to concentrate ^{131}I, and morphology on chest radiograph.[72,74,85,86]

Although some patients, especially younger ones, with distant metastases survive for decades, about 50% die within 5 years regardless of tumor histology.[40] Even so, some pulmonary metastases are compatible with long-term survival. For example, one study found that when distant metastases were confined to the lung, more than 50% of the patients were alive and free of disease at 10 years, whereas no patients with skeletal metastases survived that long.[87] The survival rates are highest in young patients with diffuse lung metastases seen only on ^{131}I imaging and not on x-ray,[86,87] which appears to be the most important feature governing an improved survival rate and prolonged disease-free interval with lung metastases.[88] Prognosis is worse with large pulmonary metastases that do not concentrate ^{131}I and is intermediate with small nodular metastases that are seen on radiographs but that do concentrate ^{131}I.[72,74,85]

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.[38,44,64,89] When applied to the papillary carcinoma data from the Mayo Clinic, 4 of the schemes using age (EORTC [European Organization for Research and Treatment of Cancer], TNM 5th edition [tumor, node, metastasis], AMES [Age, Metastases, Extent, and Size], and AGES [Age, tumor Grade, Extent, and Size]) were effective in separating low-risk patients (in whom the 20-year, cancer-specific mortality was 1%) from high-risk patients (in whom the 20-year, cancer-specific mortality was 30% to 40%).[78] With incrementally worsening MACIS (Metastasis, Age, Completeness of resection, Invasion, and Size) scores of less than 6, 6 to 6.99, 7 to 7.99, and 8+; however, the 20-year survival rates decreased from 99% to 89%, 56%, and 24%, respectively.[44] It is noteworthy that only "Completeness of resection" is subject to intervention, and its contribution to prognosis is small.

Unfortunately, a study that classified 269 patients with papillary carcinoma according to 5 different prognostic paradigms found that some patients in the lowest risk group from each approach died of cancer.[47] This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk.[64,90] The AJCC TNM staging approach (see Table 1), which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 45 years as stage I or stage II, even those with distant metastases. Although it predicts cancer mortality reasonably well,[91,92] TNM staging was not established as a predictor of recurrence and therefore does not forecast accurately the recurrences that often occur in patients who develop thyroid cancer when they are young. Currently, no prognostic systems address variants of papillary and follicular carcinoma whose clinical behavior affects outcome. Two studies have demonstrated the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.[38,93]

Differentiated thyroid cancer staging systems are certainly of value in epidemiology studies and as tools to stratify patients for prospective trials.[94] Staging systems, which are designed to segregate patients on the basis of survival, offer gross indications of prognosis for groups of patients but probably are of far less utility in determining treatment for individual patients. When treating differentiated thyroid cancer, where most patients do not succumb to cancer, many clinicians have placed a stronger emphasis on potential morbidity than on mortality.

Systems designed to predict survival provide little guidance with respect to morbidity sustained by patients who are likely to be cured by their treatments. Although the TNM classification of the AJCC and International Union Against Cancer (UICC) is universally available and widely accepted for other disease sites, the NCCN Thyroid Carcinoma Guidelines do not use TNM stages to guide therapy. Instead, many tumor and patient characteristics play important roles in these NCCN guidelines. Many specialists in thyroid cancer also follow this paradigm. Several international surveys, including one by the clinical members of the American Thyroid Association, indicate that most clinicians do not factor age into their therapeutic decisions.[95,96] This view is held by most participants in this NCCN Thyroid Carcinoma Panel.

Surgical Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total or Near-Total Thyroidectomy

The continuing debate surrounding the appropriate extent of thyroid resection reflects the limitations of prognostic scoring[46] and the morbidity often associated with total thyroidectomy performed outside of referral centers. For example, Hay and colleagues reported in 1987 that patients treated at the Mayo Clinic for low-risk papillary thyroid carcinomas (MACIS score 3.99 or less) had no improvement in survival

rates after undergoing procedures more extensive than ipsilateral lobectomy and, accordingly, concluded that more aggressive surgery was indicated only for those with higher MACIS scores.[97] In 1998, however, that center reported the results of a study designed to compare cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy. The study involved patients with papillary carcinoma considered to be low risk by AMES criteria.[98] The investigators found no significant differences 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. On the basis of these observations, Hay and colleagues concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk papillary carcinoma.[98]

Most NCCN panel members (and other authors) advise total or near-total thyroidectomy for all patients in whom the diagnosis of thyroid carcinoma is assigned preoperatively,[12,20,99] because, while they have little influence on deaths from cancer, such procedures are associated with improved disease-free survival, even in children and adults with low-risk tumors.[35,48,98,100] Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe[40,97] with an overall long-term recurrence rate of more than 30% (versus 1% after total thyroidectomy and ^{131}I therapy)[9] and the highest frequency (11%) of subsequent pulmonary metastases.[101] Higher recurrence rates are also observed with cervical lymph node metastases and multicentric tumors, providing some additional justification for more complete initial thyroid resection.[9] However, some prominent thyroid cancer specialists (including some at NCCN institutions) oppose this view and advocate unilateral lobectomy for most patients with papillary and follicular thyroid carcinoma on the basis of both the low mortality among those patients categorized as low risk by the AMES and other prognostic classification schemes (ie, most patients) and of the high complication rates reported with more extensive thyroidectomy.[45,89,102] The large thyroid remnant, however, may complicate long-term follow-up with serum thyroglobulin (Tg) determinations, and it will frustrate whole-body ^{131}I scans. In most clinical settings, decisions surrounding the extent of thyroidectomy should be individualized and undertaken in consultation with the patient. Circumstances in which unilateral thyroidectomy is inadvisable are detailed in the guidelines.

NCCN panelists believe that total lobectomy alone is adequate treatment for papillary microcarcinomas provided the patient has not been exposed to radiation, has no other risk factors, and has a tumor smaller than 1 cm that is unifocal and confined to the thyroid without vascular invasion.[9,75,76] The same is true for minimally invasive follicular cancers (see FOLL-1).

Completion Thyroidectomy

This procedure is recommended when remnant ablation is anticipated or if long-term follow-up with serum Tg determinations with or without whole-body ^{131}I scans are planned. Large thyroid remnants are difficult to ablate with ^{131}I.[101] Completion thyroidectomy has a comparable net complication rate 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.[79,103-107] In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.[105]

Miccoli and colleagues studied irradiated children from Chernobyl who developed thyroid carcinoma and were treated by lobectomy; they found that 61% had unrecognized lung or lymph node metastases that could only be identified after completion thyroidectomy.[48] In another

study, patients who underwent completion thyroidectomy within 6 months of their primary operation developed significantly fewer lymph node and hematogenous recurrences, and they survived significantly longer than did those in whom the second operation was delayed for more than 6 months.[106]

Surgical Complications

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury. These complications occur with much higher frequency after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults[108] and still more common in children[48,109] undergoing total thyroidectomy. However, the rates of persistent hypocalcemia are reported to be much lower, at least in the hands of experienced thyroid surgeons. In a review of 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.[110] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[111]

When experienced surgeons perform the operations, complications occur at a lower rate. A study of 5860 patients treated in the state of Maryland found that surgeons who performed more than 100 thyroidectomies a year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies a year had 4 times as many complications.[112]

Radioactive Iodine

Adjuvant Radioiodine Therapy

Postoperative ^{131}I thyroid remnant ablation is performed when the patient has a tumor with the potential for recurrence.[113] Studies demonstrate decreased recurrence and disease-specific mortality when postoperative ^{131}I therapy is administered as part of the initial treatment, but the supportive data are largely confined to higher risk populations.[9,39,47,114,115] In a study assessing outcomes in 1004 patients with differentiated thyroid carcinoma, tumor recurrence was about 3-fold higher in patients either treated with thyroid hormone alone or given no postoperative medical therapy when compared with patients who underwent postoperative thyroid remnant ablation with ^{131}I (P<.001). Moreover, fewer patients developed distant metastases (P<.002) after thyroid remnant ^{131}I ablation than after other forms of postoperative treatment; however, this effect is observed only in patients with primary tumors 1.5 cm or more in diameter.[114] Some find that remnant ablation has less of a therapeutic effect, perhaps, because more extensive loco-regional surgery had been done.[78]

Debate continues about ablating the thyroid bed with ^{131}I after near-total thyroidectomy.[78,114] Proposed mechanisms by which remnant ablation may decrease recurrences and disease-specific mortality include the ablation of normal tissue destined to become malignant, ablation of residual microscopic malignancy in the remnant, ablation of residual microscopic malignancy outside the remnant, ablation of residual malignancy outside the remnant obscured by uptake in a large thyroid remnant, and the demonstration of unsuspected residual malignancy on the post-therapy scan, which alters disease stage and promotes further patient management. Other reasons favoring remnant ablation include (1) simplified patient follow-up, because elimination of “thyroid bed” uptake eliminates misinterpretation of it as disease; (2) remnant ablation eliminates normal tissue as a source of Tg production, which facilitates identification of patients who are free of disease and may simplify their care while promoting early identification of those with residual cancer; and (3) elimination of normal tissue may eliminate the nidus for continued confounding anti-Tg antibody production. However, long-term evaluation of recurrence risk after adjuvant radioiodine may be confounded by the accompanying improved specificity of diagnostic testing after elimination of the thyroid remnant and by the possibility

that patients who receive adjuvant therapy may be more likely to undergo more intensive follow-up testing.

Diagnostic Whole-Body Scans and Thyroid Stunning

Whole-body ^{131}I scans are often performed after surgery to assess the completeness of thyroidectomy and the presence of residual disease. However, a phenomenon termed "stunning" may occur when scanning doses of ^{131}I induce follicular cell damage. Stunning decreases uptake in the thyroid remnant or metastases, thus impairing the therapeutic efficacy of subsequent ^{131}I.[116]

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.[116,117] Some experts recommend that diagnostic ^{131}I scans be avoided completely with decisions based on the combination of tumor stage and serum Tg. Other experts advocate that the whole-body ^{131}I diagnostic scan may alter therapy, for example: (1) when unsuspected metastases are identified, or (2) when an unexpectedly large remnant is identified that requires additional surgery or a reduction in radioiodine dosage to avoid substantial radiation thyroiditis.[118]

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.[119] 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) has become available using simplified single time point whole body dosimetry (Kloos, personal communication). In the past, hospitalization was required to administer therapeutic doses of ^{131}I larger than 30 mCi (1110 MBq). However, hospitalization is no longer necessary in most states, because a change in federal regulations permits the use of much larger ^{131}I doses in ambulatory patients.[119]

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 about 100 to 175 mCi (3700 to 6475 MBq) of ^{131}I. Cancer growing through the thyroid capsule and incompletely resected is treated with 150 to 200 mCi (5550 to 7400 MBq). Patients with distant metastases are usually treated with 200 mCi (7400 MBq) of ^{131}I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted safety limits to the blood in the elderly and in those with impaired kidney function.[120,121] Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of ^{131}I (which is very uncommon) are treated with 150 mCi of ^{131}I (5550 MBq) or less to avoid lung injury, which may occur when more than 80 mCi remain in the whole body 48 hours after treatment.

Quantitative Tumor ^{131}I Dosimetry

A second method is to use quantitative dosimetry methods to estimate the amount of radiation delivered to the lesion per unit of ^{131}I administered. This approach is attractive, because radiation exposure from arbitrarily fixed doses of ^{131}I can vary substantially. If the calculated dose to the tumor is less than 3500 cGy, it is unlikely that the cancer will respond to ^{131}I therapy.[119,122] Radioiodine activities that deliver more than 30,000 cGy to the residual normal tissue and more than 8000 cGy to metastatic foci are likely to be effective. It is necessary to serially measure the radiation activity in the target using a tracer dose and to estimate the tumor size to make these calculations,

which is difficult to do and is impossible in the setting of diffuse or microscopic lung metastases.

Blood ^{131}I Dosimetry

A third method is to administer a dose calculated to deliver a maximum of 200 cGy to the blood, while keeping the whole-body retention less than 120 mCi (4440 MBq) at 48 hours or less than 80 mCi (2960 MBq) when there is diffuse pulmonary uptake.[123] Thyroid cancer dosimetry and radioiodine therapy with doses above 200 mCi are best done in medical centers with experience using these treatments.

Post-Treatment ^{131}I Scans

When ^{131}I therapy is given, a whole-body radioiodine scan should be performed several days later to document ^{131}I uptake by the tumor. The post-treatment whole-body radioiodine scan should be done primarily because up to 25% of such scans show lesions that may be clinically important that were not detected by the diagnostic scan.[119] In a study of pre-treatment and post-treatment scans, the 2 differed in 27% of the treatment cycles, but only 10% of the post-treatment scans showed clinically significant new foci of metastatic disease.[124] Post-treatment scans were most likely to reveal clinically important new information in patients younger than 45 years who had received ^{131}I therapy in the past. Conversely, in older patients and patients who had not previously received ^{131}I therapy, the post-treatment scans rarely yielded new information that might have altered the patient's prognosis.[124] Thus, the NCCN panel only gives a category 2B recommendation for post-treatment radioiodine scanning.

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.[125] In contrast, neither serum Tg or whole-body radioiodine 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.[126,127] Using current Tg assays, patients with measurable serum Tg levels during TSH suppression and those with stimulated Tg levels more than 2 ng/mL are likely to have residual/recurrent disease that may be localized in almost 50% promptly and in an additional 30% over the next 3-5 years.[128] About 6% of patients with detectable serum Tg levels, which are less than 2 ng/mL after stimulation, have recurrences over the next 3-5 years, while this is true for about 2% of patients with completely undetectable serum Tg after stimulation. Conversely, the long-term clinical significance is uncertain for disease only detected by minimally elevated Tg levels after stimulation.

Recombinant Human TSH

During follow-up, periodic withdrawal of thyroid hormone therapy has traditionally been required to increase the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements (with or without ^{131}I scanning) 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.[129]

A second multicenter international study was performed to assess the effects of 2 rhTSH dosing schedules on whole-body ^{131}I scans and serum Tg levels when compared with scans and Tg levels obtained after thyroid hormone withdrawal. The scanning method in this study was more carefully standardized and took into account the fact that ^{131}I

retention was higher in patients rendered hypothyroid than in patients given rhTSH.[127] Scans were concordant in 89% of the patients and superior in 4% of the patients 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 scanning and serum Tg measurements detected 100% of metastatic carcinoma.[127] 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. A whole-body scan and Tg measurements were performed on the fifth day. Whole-body ^{131}I images were acquired after 30 minutes of scanning or after obtaining 140,000 counts, whichever came first. A serum Tg of 2.0 ng/mL or higher obtained 72 hours after the last rhTSH injection indicates that thyroid tissue or thyroid carcinoma is present, regardless of the whole-body scan findings.[127,130]

Recombinant human TSH is well tolerated. Nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects.[127] It is associated with significantly fewer symptoms and dysphoric mood states than hypothyroidism induced by thyroid hormone withdrawal.[129]

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 ^{131}I scanning.[126-128,131,132] 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 ^{131}I scans stipulate using 4-mCi ^{131}I doses (based on the doses used in the pivotal phase III trial)[127] and a scanning 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).[133,134] It is therefore recommended that patients undergo Tg monitoring via the same Tg assay performed in the same laboratory. Ideally, serum is frozen and saved for future analyses if needed, especially should a change in Tg assay be necessary.

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.[135] These antibodies typically falsely lower the Tg value in immunochemiluminometric assay (ICMA) and immunoradiometric (IRMA) assays, while raising the value in older radioimmunoassay (RIA). Although the clinical importance of these antibodies is unclear, their persistence for more than 1 year or so after thyroidectomy and radioiodine ablation probably indicates the presence of residual thyroid tissue and possibly an increased risk of recurrence.[135] In one study, 49% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of 100 U/mL or more had a recurrence when compared with only 3% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of less than 100 U/mL.[136] In patients with co-existent autoimmune thyroid disease at the time of surgery, anti-Tg antibodies may persist far longer. In a study of 116 patients with anti-Tg antibodies before thyroidectomy, antibodies remained detectable for up to 20 years in some patients without detectable thyroid tissue, and the median time to disappearance of antibodies was 3 years.[137]

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 [NIS], TSH receptor, and Tg mRNAs) or DNA-based strategies to detect thyroid oncogenes in peripheral blood, represent current areas of active research that may improve the detection of residual cancer and the monitoring of these patients, especially during thyroxine treatment or when circulating anti-Tg antibodies are present.[138,139]

Treating Tg-Positive/Scan-Negative Patients

Post-treatment ^{131}I scans may yield localizing information when the serum Tg level is increased, but a tumor cannot be found by physical examination or localizing techniques (such as diagnostic ^{131}I scans, neck ultrasonography, computed tomography [CT], magnetic resonance imaging [MRI], or PET). Pulmonary metastases may be found only after administering therapeutic doses of ^{131}I and obtaining a whole-body scan within a few days of treatment.[140] In a study of 283 patients treated with 100 mCi (3700 MBq) of ^{131}I, 6.4% had lung and bone metastases detected after treatment that had been suspected on the basis of high serum Tg concentrations alone but had not been detected after 2-mCi (74 MBq) diagnostic scans.[141]

In another study, all but 1 of 17 patients with increased serum Tg concentrations and negative 5-mCi (185 MBq) diagnostic scans showed ^{131}I uptake after 75 to 140 mCi (2775 to 5180 MBq) of ^{131}I; more than 50% of these patients had lung metastases.[142]

Unfortunately, most diagnostic scan–negative/Tg-positive patients are not rendered disease free by ^{131}I therapy; however, the tumor burden may be diminished.[143] For this reason, most patients with residual or recurrent disease confined to the neck undergo re-operation rather than radioiodine therapy in the hopes of a higher chance for cure. Radioiodine therapy is more commonly considered for those with distant metastases or inoperable local disease. Patients not benefiting from this therapy can be considered for clinical trials, especially those patients with progressive metastatic disease. When a large tumor is not visible on a diagnostic whole-body scan, this implies that its ^{131}I concentrating ability per gram of tissue is very low and hence a lack of response to ^{131}I therapy may be anticipated.

The Tg level recommended for empiric treatment has been decreasing; it was approximately 30 or 40 ng/mL about a decade ago, but now it is approximately 10 ng/mL.[140,144] However, no study has yet demonstrated any decrease in morbidity or mortality in patients treated with ^{131}I on the basis of increased Tg measurements alone. In a long-term follow-up study, no suggestion of a survival advantage was associated with empiric high-dose radioiodine in scan-negative patients.[145] Further, potential long-term side effects (such as xerostomia, nasolacrimal duct stenosis, bone marrow and gonadal compromise, and the risk of hematologic and other malignancies) may negate any benefit.[113,146]

Thyroid Hormone Suppression of TSH

Decreased recurrence and cancer-specific mortality rates for differentiated thyroid carcinoma are reported by some authors for patients treated with thyroid hormone suppressive therapy.[9,114,147-151] The average dosage needed to attain serum TSH levels in the euthyroid range is higher in patients with thyroid carcinoma (2.11 mcg/kg per day) than in those patients with spontaneously occurring primary hypothyroidism (1.62 mcg/kg per day)[150] and still higher doses are required to suppress serum TSH in thyroid carcinoma patients. Still, the optimal TSH level to be achieved in patients with thyroid carcinoma is uncertain. Superior outcomes were associated with aggressive thyroid hormone suppression therapy in high-risk patients but were achieved with modest suppression in stage II patients.[151] Excessive TSH suppression (into the undetectable, thyrotoxic range) is not required to prevent disease progression in all patients with differentiated thyroid cancer. As a practical matter, the most appropriate dose of thyroid hormone for most low-risk patients with differentiated thyroid carcinoma is the dose that decreases the serum concentration

to just below the lower limit of the normal range for the assay being used. A greater degree of suppression is generally recommended for higher risk patients.

Adjuvant External-Beam Radiation Therapy

No prospective controlled trials have been completed using adjuvant external-beam RT. An attempt to perform such a study encountered marked resistance to randomization among most patients eligible to participate in such a trial.[152] One retrospective study demonstrated a benefit of adjuvant external-beam RT after radioactive iodine in patients older than 40 years who have invasive papillary thyroid cancer (T4) and lymph node involvement (N1).[153] Local recurrence and locoregional and distant failure were significantly improved. A second study demonstrated improved cause-specific survival and local relapse-free rate in selected patients treated with adjuvant external-beam RT (in addition to total thyroidectomy and TSH-suppressive therapy with thyroid hormone) for papillary thyroid carcinoma with microscopic residuum. Not all patients received radioactive iodine therapy.[39] 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 receiving external RT (90%) than when not receiving it (26%).[154] In another study, patients with microscopically invasive follicular carcinoma after surgery were also more often disease free when postoperative external RT is given (53%) than when it is not given (38%).[154] However, these patients had not received radioactive iodine. Similar benefit was shown with radioactive iodine alone in comparable patients treated with radioactive iodine after surgery.[154]

Chemotherapy, External-Beam Radiation, and Surgical Excision of Metastases

Focal lesions that do not concentrate ^{131}I adequately and isolated skeletal metastases should be considered for surgical excision or external irradiation. Brain metastases pose a special problem, because ^{131}I therapy may induce cerebral edema. Once brain metastases are diagnosed, disease-specific mortality is very high (67%), with a reported median survival of 12.4 months in one retrospective study. Survival was significantly improved by surgical resection of one or more tumor foci.[155]

Life-threatening tumors refractory to all other forms of therapy may be palliatively treated with doxorubicin, although the response rate is poor.[40] The experience with chemotherapy in patients with differentiated thyroid carcinoma is limited, because most recurrent tumors respond well to surgery, ^{131}I therapy, or external-beam RT. Chemotherapy's main use has been 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 had objective responses.[156] In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.[157] Combination chemotherapy is not clearly superior to doxorubicin therapy alone.[40] Overall, traditional cytotoxic systemic chemotherapy (eg, doxorubicin) has minimal efficacy in patients with metastatic differentiated thyroid disease.

Several phase II trials have been initiated to evaluate novel treatments for patients with metastatic differentiated thyroid carcinoma. The first to be completed and published was a phase II study of celecoxib (400 mg twice daily) in patients with progressive, radioiodine-unresponsive disease.[158] Although 12-month progression-free survival was only 3%, 38% of the patients had stable disease, representing a possible alteration in their disease course. Currently, other agents are in clinical trials, including (1) multitargeted kinase inhibitors, such as motesanib diphosphate (AMG-706),[159,160] sorafenib,[161, 162] sunitinib,[163] axitinib,[164]

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, 17-allylamino-17-demethoxygeldanamycin (17-AAG); (5) the proteasome inhibitor, bortezomib; and (6) a derivative of thalidomide, lenalidomide.[165,166]

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 is recommended if not previously done. A lateral neck ultrasound can also be considered (category 2B). 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.[167] A chest x-ray can be considered. The recommendation from the guidelines panel to evaluate vocal cord mobility was one of nonuniform consensus (category 2B).

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 PAP-1). However, there was not uniform consensus about the preferred primary surgery for patients who are assumed to be at lower risk of cancer-specific mortality. The majority of panel members opted for total thyroidectomy (category 2B) in any patient in whom papillary thyroid carcinoma was identified preoperatively or at the time of surgery. However, a minority of panel members felt strongly that, initially, lobectomy plus isthmusectomy (category 2B) is adequate surgery for patients at lower risk. A study in more than 5000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for both low- and high-risk patients.[168] For patients who undergo lobectomy plus isthmusectomy (lower risk patients), completion of thyroidectomy is warranted for aggressive variant disease, macroscopic multifocal disease, positive isthmus margins, cervical lymph node metastases, or extrathyroidal extension. Note that *aggressive variant disease* is defined as tall cell, columnar cell, insular, oxyphilic, or poorly differentiated features.

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

Radioactive Iodine

Postoperative Whole-Body ^{131}I Diagnostic Scans

Performing a diagnostic whole-body ^{131}I scan with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before ^{131}I therapy is a category 2B recommendation. The panel advises that this decision should be weighed against the problem of stunning that occurs with diagnostic ^{131}I scans.[169] A diagnostic whole-body ^{123}I scan does not carry a risk of stunning. The alternatives to performing a diagnostic ^{131}I scan are to obtain an ^{123}I scan before ^{131}I therapy, obtain a thyroid uptake measurement with microcurie quantities of radioiodine to confirm neck uptake, or forgo the diagnostic scan. If radioiodine is

administered after a diagnostic ^{131}I study, the time interval between radioiodine doses should be minimized. Whenever therapeutic radioiodine is administered, a whole-body scan should be obtained about 5 to 8 days after treatment with ^{131}I, which is termed a "post-treatment ^{131}I scan" 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. Panel members debated about the use of ^{131}I to ablate uptake in the thyroid bed after total thyroidectomy. Ablation may be appropriate for patients after thyroidectomy if they have nodal metastases, distant metastases, aggressive histology, or their initial lesion was 1 cm or more in size (see PAP-3). There was nonuniform consensus (category 2B) for adjuvant radioiodine ablation (30-100 mCi) of the thyroid bed for suspected (based on pathology, postoperative Tg, and intraoperative findings) or proven thyroid bed uptake in patients who have had total thyroidectomy (see PAP-4). Empiric administration of radioiodine without a diagnostic scan is not routinely recommended by the NCCN panel.

Radioactive Iodine Treatment

Therapy with ^{131}I is advised for patients with tumors found on examination, imaging studies, or by increased serum Tg levels if these tumors are not amenable to surgical removal and if they concentrate ^{131}I. 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 child-bearing potential. The panel agrees that radioiodine treatment is not needed for patients with Tg levels less than 1 ng/mL, negative radioiodine scans, and negative anti-Tg antibodies. For patients with suspected or proven radioiodine avid residual tumor, radioiodine treatment can be given at 100 to 200 mCi along with a post-treatment scan or dosimetry can be considered for distant metastases (see PAP-4).

For unresectable locoregional recurrence, radioiodine treatment with RT can be given if the radioiodine scan is positive; RT alone is another option in the absence of radioiodine uptake. When recurrent disease is suspected based on a high serum stimulated Tg values (more than 10 ng/mL) and based on negative imaging studies (including PET scans), radioiodine therapy can be considered (category 3) using an empiric fixed dose of 100 to 150 mCi of ^{131}I (see PAP-5); 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 location(s) (eg, solitary CNS, bone, or other extracervical sites) (see PAP-6).

Adjuvant External-Beam Radiation Therapy

The guidelines recommend that external RT be considered for patients older than 45 years with T4 (surgically evident extra-thyroidal invasion) and without gross residual disease in their neck.

Thyroxine Suppression of TSH

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

Surveillance and Maintenance

Patients should receive an annual follow-up radioiodine scan until no radioactive iodine avid tumor is evident if they have detectable Tg, distant metastases, or soft tissue invasion on initial staging. Low-risk, stage I and II patients no longer require routine radioiodine scans if they have negative stimulated Tg, negative neck ultrasound, and no longer have clinical disease. A subgroup of very low-risk patients (micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic ultrasound followup, without stimulated Tg or followup whole-body scanning, as long as the basal Tg remains low. The guidelines recommend the following (see PAP-5): (1) long-term surveillance and maintenance with a physical examination, TSH, Tg, and anti-Tg antibodies measurements every 6 to 12 months, then annually if patients remain disease free; (2) periodic neck ultrasound; (3) TSH–stimulated Tg at 12 months (without radioiodine scan) in patients previously treated with radioiodine with recent negative neck ultrasound and with undetectable TSH-suppressed Tg (anti-Tg antibody negative) with T1-2, N0-1, M0 on initial staging; (4) regular diagnostic whole-body ^{131}I scans every 12 months until no response is seen to radioiodine treatment in iodine avid tumors (either withdrawal of thyroid hormone or rhTSH) for patients with detectable Tg, distant metastases, or soft tissue invasion on initial staging; and (5) consider additional nonradioiodine imaging for patients whose ^{131}I scans are negative and stimulated Tg is more than 2 to 5 ng/mL (eg, FDG PET with or without CT if Tg levels are 10 ng/mL or more). The panel acknowledges that the suggested Tg cutoff levels will continue to evolve as new Tg assays are introduced.

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 PAP-5). For unresectable locoregional recurrences, ^{131}I therapy is recommended for tumors that concentrate ^{131}I (that is, radioiodine scan positive), and external-beam RT alone is recommended for those that do not concentrate ^{131}I (that is, radioiodine scan negative). Unresectable iodine avid locoregional disease that is unlikely to respond to radioiodine therapy alone may additionally be treated with external-beam RT. For extra-cervical metastatic disease, several therapeutic approaches are recommended (see PAP-6), depending on the site and number of tumor foci. For skeletal metastases, surgical palliation is recommended for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are ^{131}I treatment (if the whole-body scan is positive) 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; embolization of metastases can also be considered.[170] 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 scan is positive (with consideration of dosimetry to maximize dosing), and/or image-guided RT (see NCCN Central Nervous System Cancers). For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred. For other extracervical sites, surgical resection of selected, enlarging, or symptomatic metastases can be considered; for other disseminated tumors, ^{131}I is recommended if the tumor concentrates the radioisotope (with consideration of dosimetry to maximize the dosing), systemic therapy if the patient is not in a clinical trial, or best supportive care.[171] Because chemotherapy has been generally disappointing, the guidelines recommend clinical trials for non-radioiodine avid tumors reserving sorafenib or traditional cytotoxic systemic therapy for progressive or symptomatic disease if a trial is not available.[20,161,162] There are several agents in clinical trials (www.thyroidtrials.org, http://www.nci.nih.gov/clinicaltrials).

Follicular Thyroid Carcinoma

Because the diagnosis and treatment of papillary and follicular carcinoma are similar, only the important differences in the management of follicular carcinoma are highlighted. FNA is not as specific for follicular thyroid carcinoma as it is for papillary carcinoma and accounts for the main differences in management of the 2 tumor types. The FNA cytologic diagnosis of "follicular neoplasm" will prove to be a benign follicular adenoma in 80% of cases. However, 20% of patients with "follicular neoplasms" are ultimately diagnosed with follicular thyroid carcinoma when the final pathology is assessed. Further diagnostic and treatment decisions for patients who present with follicular neoplasms are based on their TSH levels (see THYR-2). The diagnosis of follicular carcinoma requires evidence for transcapsular nodule invasion or vascular invasion. Because most patients with "follicular neoplasms" have benign disease, total thyroidectomy is recommended only if invasive cancer or metastatic disease is apparent at the time of surgery or if the patient opts for total thyroidectomy to avoid a second procedure if cancer is found at pathologic review. Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery. If invasive follicular carcinoma (extensive vascular invasion) is found on the final histologic sections after lobectomy plus isthmusectomy, prompt completion of thyroidectomy is recommended (see FOLL-1).

Completion thyroidectomy should be considered for tumors that, on final histologic sections after lobectomy plus isthmusectomy, are minimally invasive follicular carcinomas. *Minimally invasive* cancer is characterized as a well-defined tumor with microscopic capsular and/or a few foci of vascular invasion and often requires examination of at least 10 histologic sections.[172] These tumors may also be simply followed carefully, because minimally invasive follicular carcinomas have an excellent prognosis. However, deaths attributed to minimally invasive follicular carcinoma do occasionally occur. For patients who have a central neck recurrence, preoperative vocal cord assessment should be considered (see FOLL-4).

The other features of management and follow-up for follicular carcinoma are identical to those of papillary carcinoma with the exception that adjuvant RT is not used as an adjuvant measure postoperatively for advanced lesions (ie, T4). However, RT is used for nonresectable growing disease in the neck. As is done for papillary carcinoma, adjuvant radioiodine ablation of the thyroid bed (category 2B) can be used for suspected or proven thyroid bed uptake. Radioiodine treatment and post-treatment scan (with consideration of dosimetry for distant metastasis) may be administered for suspected or proven radioiodine avid residual tumor (see FOLL-3). The decision to perform a diagnostic whole-body ^{131}I scan with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) before ^{131}I therapy is administered is a category 2B recommendation for both follicular and papillary carcinoma.

Hürthle Cell Carcinoma

This tumor (also known as oxyphilic cell carcinoma) is usually assumed to be a variant of follicular thyroid carcinoma, although the prognosis of Hürthle cell carcinoma is worse.[173,174] The Hürthle cell variant of papillary carcinoma is rare and seems to have a prognosis similar to follicular thyroid carcinoma.[175] The management of this Hürthle cell 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, or prophylactic (category 2B) central neck compartment dissection may be considered; 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 HÜRT-4).

Adjuvant RT can be considered postoperatively for advanced Hürthle lesions (ie, T4) (see HÜRT-3), similar to the management for papillary carcinoma. Nonetheless, adjuvant radioiodine therapy has been reported to decrease the risk of locoregional recurrence and is recommended for unresectable disease with positive radioiodine scans. Radioiodine therapy (100-150 mCi) should be considered (category 2B) after thyroidectomy for patients with stimulated Tg levels of more than 10 ng/mL and scan negative (including FDG-PET) (see HÜRT-4).[70] The panel recommends (category 2B) that a diagnostic whole-body ^{131}I scan with adequate TSH stimulation (thyroid withdrawal or rhTSH stimulation) be performed before ^{131}I therapy is administered. Postoperative RT may be used for advanced lesions.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) derives from the neuroendocrine parafollicular or C cells of the thyroid.[176] Sporadic MTC accounts for 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, or familial MTC.[177,178] Because the C cells are predominantly located in the upper portion of each thyroid lobe, patients with sporadic disease typically present with upper pole nodules. Metastatic cervical adenopathy appears in about 50% of patients at initial presentation. Symptoms of upper aerodigestive tract compression or invasion are reported by up to 15% of patients with sporadic disease.[179]

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

Nodule Evaluation and Diagnosis

Patients with medullary carcinoma can be identified by using pathologic diagnosis or by prospective genetic screening. Separate paths are included in the guidelines algorithm (see MEDU-1) depending on the method of identification used.

Sporadic MTC is usually suspected after FNA of a solitary nodule. Routine measurement of the serum calcitonin concentration is not recommended as a screen for MTC in a patient with a solitary nodule. However, reports suggest that perhaps as many as 3% of patients with nodular thyroid disease will have an increased serum calcitonin level when measured by a sensitive immunometric assay; 40% of these patients will prove to have MTC at thyroidectomy.[180-182] Routine measurement of the serum calcitonin concentration is not recommended for evaluating a patient with nodular thyroid disease because of the expense of screening the many existing thyroid nodules to find the few cases of MTC, the lack of confirmatory pentagastrin stimulation testing, and the resulting need for thyroidectomy in some patients who will ultimately be found to have benign thyroid disease.[183,184]

For patients in known kindreds with inherited MTC, prospective family screening with testing for mutant ret genes can identify disease carriers long before clinical symptoms or signs are noted.[185] The traditional approach of stimulating secretion of calcitonin by either pentagastrin or calcium infusion is no longer recommended, because elevated calcitonin is not a specific or adequately sensitive marker for MTC[186] and because pentagastrin is no longer available in the United States.

Serum intact parathyroid hormone levels and calcium levels are measured when inherited disease is suspected (see MEDU-3). Compared with sporadic disease, the typical age of presentation for familial disease is the third decade, without gender preference. In MEN 2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening. All familial forms of MTC and MEN 2 are inherited in an autosomal dominant fashion.

Mutations in the *RET* proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of familial MTC.[185,187] The *RET* proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations associated with MEN 2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13, whereas MEN 2B and some familial MTC mutations are found within the intracellular exons 14-16 (see Table 2). Somatic mutations in exons 11, 13, and 16 have also been found in at least 25% of sporadic MTC tumors, particularly the codon 918 mutation that activates the tyrosine kinase function of the receptor and is associated with poorer patient prognosis. About 6% of patients with clinically sporadic MTC carry a germline mutation in *RET*, leading to identification of new kindreds with multiple previously undiagnosed affected individuals.[188] Genetic testing for *RET* proto-oncogene mutations should be encouraged for all newly diagnosed patients with clinically apparent sporadic MTC, and for screening children and adults in known kindreds with inherited forms of MTC; genetic counseling should be considered.

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

Staging

Compared with differentiated thyroid carcinoma, a smaller set of staging approaches exist for MTC. The TNM criteria for clinicopathologic tumor staging are based on tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (see Table 1) (6th edition AJCC staging manual).[64] An MTC less than 2 cm in diameter without evidence of disease outside of the thyroid gland is classified as stage I. Any larger tumor (more than 2 cm but 4 cm or less) limited to the thyroid without nodal or distant metastases is classified as stage II. The presence of level 6 nodal metastases, minimal extrathyroidal invasion, or tumor size greater than 4 cm places the patient in stage III. Tumor extending beyond the perithyroid soft tissues, involving lymph nodes beyond level 6, or spreading to distant metastatic sites is classified as stage IV.

Note that all follow-up studies (discussed in this manuscript) reporting on AJCC-TNM staging have referred to the 5th edition[65] and not the 6th edition.[64] In one study with a median follow-up period of only 4 years, mortality from MTC was 0% for stage I, 13% for stage II, 56% for stage III, and 100% for stage IV disease.[189] An alternative staging classification proposed by DeGroot defines stage I disease as localized

to the thyroid and stage II as limited to the thyroid or locoregional nodes.[190] Extrathyroidal or extranodal extension characterizes stage III disease, and distant metastases characterize stage IV. Using this approach, survival significantly declines with increasing stage assignment. In particular, the presence of either stage III or stage IV disease increases the risk of death from MTC at least 7-fold and carries a median disease-specific survival of 3 to 5 years.[179] A third approach, used by the National Thyroid Cancer Treatment Cooperative Study Group,[38] defines stage I disease as the premalignant lesion C-cell hyperplasia, generally only identified as an incidental finding except as a result of familial screening. Stage II disease is a primary tumor less than 1 cm without locoregional or distant metastasis. Stage III is a tumor greater than 1 cm or locoregional nodal metastasis. The presence of distant metastases defines stage IV disease.

However, these staging classifications lack other important prognostic factors. Notably absent is the age at diagnosis. Patients younger than 40 years at diagnosis have a 5- and 10-year disease-specific survival rate of about 95% and 75%, respectively, compared with 65% and 50% for those older than 40 years.[179] Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically are diagnosed at an earlier age) is probably similar to those with sporadic disease.[191,192] Despite an even younger typical age at diagnosis; however, patients with MEN 2B who have MTC are more likely than those with either MEN 2A or familial MTC to have locally aggressive disease.[192] Other factors that may be important for predicting a worse prognosis include: (1) the heterogeneity and paucity of calcitonin immunostaining of the tumor;[193] (2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level;[194] and (3) postoperative residual hypercalcitoninemia.[189] Improvement in the predictive value of the TNM staging may result from incorporation of disease type (sporadic versus familial) and the presence of bilateral versus unilateral adenopathy.[195] With more study, specific germline or somatic mutations in *RET* may also be useful predictors of disease outcome. Certainly, presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease.[196]

Surgical Management

Surgery is the main treatment for MTC, because there is no known curative systemic therapy for medullary carcinoma. MTC cells do not concentrate radioactive iodine, and MTC does not respond well to conventional cytotoxic chemotherapy or TSH suppression. Even with patients who have apparently sporadic disease, the possibility of MEN 2 should dictate that a *RET* proto-oncogene mutation is proven to be absent or that hyperparathyroidism and pheochromocytoma should be excluded preoperatively. Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC.[179] If a patient with inherited disease is diagnosed early enough, the recommendation is generally to perform a prophylactic total thyroidectomy by age 5 years, especially in patients with codon 609, 611, 618, 620, 630, or 634 *RET* (risk level II) mutations.[197] Total thyroidectomy is recommended in the first year of life or at diagnosis for MEN 2B patients or carriers of codon 883, 918, or 922 *RET* (risk level III) mutations. However, for patients with codon 768, 790, 791, 891, and 804 *RET* (risk level I) mutations, the lethality of MTC may be lower than with other *RET* mutations.[198] In patients with these *RET* mutations, annual provocative (calcium) calcitonin testing may be performed; total thyroidectomy and central node dissection may be deferred until tests become abnormal after the age of 5 years.[199] Delaying thyroidectomy until age 10 years may also be appropriate for children with risk level I mutations because of the late onset of MTC development.[200] A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with RET mutations for MEN 2A; longer follow-up is necessary to determine if these patients are cured.[201] Patients with pheochromocytomas must be treated

preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery on the thyroid. Forced hydration and alpha-blockade are necessary to prevent hypotension after the tumor is removed. After institution of alpha-blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and incorporation of simultaneous parathyroid resection for hyperparathyroidism. A bilateral central neck dissection (level VI) is preferred for all patients with pathologically demonstrated MTC and for those with MEN 2B. For those patients with MEN 2A who undergo prophylactic thyroidectomy, bilateral central neck dissection (level VI) should be considered if patients have an increased calcium-stimulated calcitonin test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II to V) is considered for these patients with primary tumor(s) 1 cm or larger in diameter (> 0.5 cm for patients with MEN 2B) or for patients with central compartment lymph node metastases (see MEDU-3). With a concurrent diagnosis of hyperparathyroidism in MEN 2A, the surgeon should leave or autotransplant the equivalent mass of one normal parathyroid gland if multiglandular hyperplasia is present. Cryopreservation of resected parathyroid tissue should be considered to allow future implantation in the event of iatrogenic hypoparathyroidism. Disfiguring radical node dissections do not improve prognosis and are not indicated. In the presence of grossly invasive disease, more extended procedures with resection of involved neck structures may be appropriate. Function-preserving approaches are preferred. Postoperative thyroid hormone therapy is indicated; however, TSH suppression is not appropriate, because C cells lack TSH receptors.

Adjuvant Radiation Therapy

External-beam RT has not been adequately studied as adjuvant therapy in medullary carcinoma. Slight improvements have been reported in local disease-free survival after external-beam RT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement. However, most centers do not have extensive experience with adjuvant RT for this disease. When external-beam RT is used, 40 Gy is typically administered in 20 fractions to the cervical, supraclavicular, and upper mediastinal lymph nodes over 4 weeks, with subsequent booster doses of 10 Gy in 5 fractions to the thyroid bed.[119] Adjuvant RT can be considered for patients with T4 disease whose tumors are 1.0 cm or more in diameter. As for differentiated carcinoma, external-beam RT can also be given to palliate painful or progressing bone metastases.

Persistently Increased Calcitonin

Serum concentrations of calcitonin and CEA should be measured 2 or 3 months postoperatively. About 80% of patients with palpable MTC and 50% of those with nonpalpable but macroscopic MTC who undergo supposedly curative resection have serum calcitonin values indicative of residual disease. Those patients with residual disease may benefit from further evaluation to detect either residual resectable disease in the neck or the presence of distant metastases. Patients with a basal serum calcitonin value greater than 1000 pg/mL and with no obvious MTC in the neck and upper mediastinum probably have distant metastases, most likely in the liver. However, occasionally patients have relatively low serum CEA and calcitonin levels but have extensive metastatic disease; initial postoperative staging imaging is therefore not unreasonable despite the absence of very high serum markers.

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease,

15 patients with MEN 2A, and 6 patients with MEN 2B), the 5- and 10-year survival rates were 90% and 86%, respectively.[202] Two studies have reported higher mortality rates for patients with high postoperative serum calcitonin values, with more than 50% of patients having a recurrence during a mean follow-up of 10 years.[189,203] Routine lymphadenectomy or excision of palpable tumor generally fails to normalize the serum calcitonin concentrations in such patients; therefore, some have focused attention on detection and eradication of microscopic tumor deposits with a curative intent in patients without distant metastases. Extensive dissection to remove all nodal and perinodal tissue from the neck and upper mediastinum was first reported to normalize the stimulated serum calcitonin levels in 4 of 11 patients at least 2 years postoperatively.[204] In subsequent larger studies, 20% to 40% of patients undergoing microdissection of the central and bilateral neck compartments were biochemically cured, with minimal perioperative morbidity.[205,206]

When repeat surgery is planned for curative intent, preoperative assessment should include locoregional imaging (such as ultrasonography of the neck and upper mediastinum) and attempts to exclude patients with distant metastases, which may include CT of the chest, and CT or MRI of the abdomen. Laparoscopic assessment of the liver may be performed if distant metastases are not detected by this diagnostic approach.[206] However, in the absence of long-term outcomes, application of this approach should probably be limited to those centers with experience with these patients. Other imaging procedures occasionally used include bone scintigraphy; ^{111}In-pentetreotide, 6-^{18}F-flourodopamine, and ^{18}F-FDG positron emission tomography; ^{99m}Tc pentavalent dimercaptosuccinic acid, ^{99m}Tc-sestamibi, or tetrofosmin; and systemic venous sampling by catheterization of the hepatic veins, both internal jugular veins, and the innominate veins, with measurements of serum calcitonin before and after stimulation.

Postoperative Management and Surveillance

Measurements of serum calcitonin and CEA levels are the cornerstone of postoperative assessment for residual disease (see MEDU-4). For patients with a negative calcitonin level, neck ultrasound could be considered. Patients with undetectable calcitonin levels can subsequently be followed with annual measurements of serum markers and additional studies or more frequent testing as indicated. Nonetheless, the likelihood of significant residual disease is very low in patients with a negative basal calcitonin level in a sensitive assay. If the patient has MEN 2, annual screening for pheochromocytoma (MEN 2B or 2A) and hyperparathyroidism (MEN 2A) should also be performed. For some *RET* mutations (eg, codons 768, 790, V804M, or 891), less frequent screening may be appropriate. Patients with abnormal serum markers should be considered for additional diagnostic imaging to identify the location of tumor. The panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but there is insufficient evidence to recommend any particular choice or combination of tests.

For the asymptomatic patient with abnormal markers in whom imaging fails to identify foci of disease, the panel recommends conservative annual surveillance with repeat measurement of the serum markers. Neck ultrasound scanning may be considered to examine the superior mediastinum, the bilateral central compartment, and the bilateral lateral neck compartments. For asymptomatic patients with abnormal markers and repeated negative imaging, continued observation or consideration of cervical re-operation is recommended if incomplete primary surgery was performed. For the patient with increasing serum markers, more frequent imaging may be considered. Outside of clinical trials, no therapeutic intervention is recommended on the basis of abnormal markers alone.

Recurrent or Persistent Disease

When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended with or without RT. If there is symptomatic progressive and unresectable locoregional disease, then RT is recommended. In the presence of distant metastases, palliative resection may be considered. Similarly, distant metastases that are causing symptoms (such as those in bone) could be considered for palliative resection, ablation (for example, radiofrequency, embolization, or other regional therapy) or other regional treatment (see MEDU-5). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease) but observation is acceptable, given the lack of data regarding alteration in outcome. In the setting of disseminated distant symptomatic metastases, the guidelines recommend the following: (1) clinical trial (preferred); (2) RT can be administered in the setting of focal symptoms; (3) sorafenib, which is an oral vascular endothelial growth factor receptor (VEGFR) inhibitor;[207] (4) systemic chemotherapy can be administered, using dacarbazine or combinations including dacarbazine.[85,208] (4) bisphosphonate therapy can be considered for bone metastases; and/or (5) best supportive care. In patients with metastatic medullary thyroid cancer, sorafenib reduces symptoms due to hypercalcitonemia and metastases.[207] Currently, clinical trials are ongoing, studying the effectiveness of novel multi-targeted therapies including motesanib diphosphate (AMG-706),[159] vandetanib (in inherited disease only),[209] sunitinib,[210] sorafenib,[211] and XL 184,[212] and pazopanib (GW786034). Of interest, calcitonin levels decreased dramatically after vandetanib therapy which did not directly correlate with changes in tumor volume, thus, calcitonin may not be a reliable marker of tumor volume in patients receiving RET inhibitor therapy.[213,214] A study in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with ^{131}I;[215] overall survival was improved in the subset of patients with calcitonin doubling times less than 2 years.

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinomas are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%. Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 65 years. Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[37] Approximately 50% of patients with anaplastic carcinoma have either a prior or coexistent differentiated carcinoma. Anaplastic carcinoma develops from more differentiated tumors as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor protein.[216] 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 thyroglobulin, whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, radioiodine scanning 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.[217] The lungs and pleura are the most common site of distant metastases, being present in up to 90% of patients with distant disease. About 5% to 15% of patients have bone metastases; 5% have brain metastases; and a few have metastases to the skin, liver, kidneys, pancreas, heart, and adrenal glands. All anaplastic carcinomas are considered stage IV (A, B, or C) (see Table 1). The T4 category includes: (1) T4a tumors which are intrathyroidal and surgically resectable; (2) T4b tumors which are extrathyroidal and not surgically resectable. However, clinically apparent anaplastic tumors are usually unresectable.

The diagnosis of anaplastic carcinoma is usually established by FNA or surgical biopsy. However, on occasion it can be difficult to discriminate

between anaplastic thyroid cancer and other primary thyroid malignancies (such as MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid.[218] Diagnostic procedures include a complete blood 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 aero-digestive tract structures.[219] CT images of the head, chest, abdomen, and pelvis are used to establish the extent of distant metastases. 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. The 1- and 5-year survival rates are about 25% and 5%, respectively.[217] 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.[220] 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.[220,221] External-beam RT, administered in conventional doses, also does not prolong survival. Treatment with single-drug chemotherapy also does not improve survival or control of disease in the neck, although perhaps 20% of patients have some response in distant metastases. The introduction of hyperfractionated RT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year. Distant metastases then become the leading cause of death.[222] Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin, followed by debulking surgery in responsive patients.[223] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival. Paclitaxel has been tested in newly diagnosed patients and may provide some palliative benefit.[224]

Once the diagnosis of anaplastic carcinoma is identified 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 or near-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 combretastatin A4 phosphate (CA4P) (a vascular disrupting agent), CS-7107 (an oral PPAR gamma [peroxisome proliferator-activated receptors] agonist), and novel multitargeted therapies including sorafenib and imatinib (Gleevec).[166,225] A patient with anaplastic thyroid cancer had a durable complete response in a phase I trial with CA4P, and he has been disease free for more than 3 years.[226,227]

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 such treatment and that prolonged remission is uncommonly reported. The guidelines do not recommend particular chemotherapeutic agents, either for radiosensitization or full-dose therapy, because of a lack of clear evidence of efficacy for any particular regimen.

Disclosures for the NCCN Thyroid Carcinoma Guidelines Panel

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Figure 1:

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

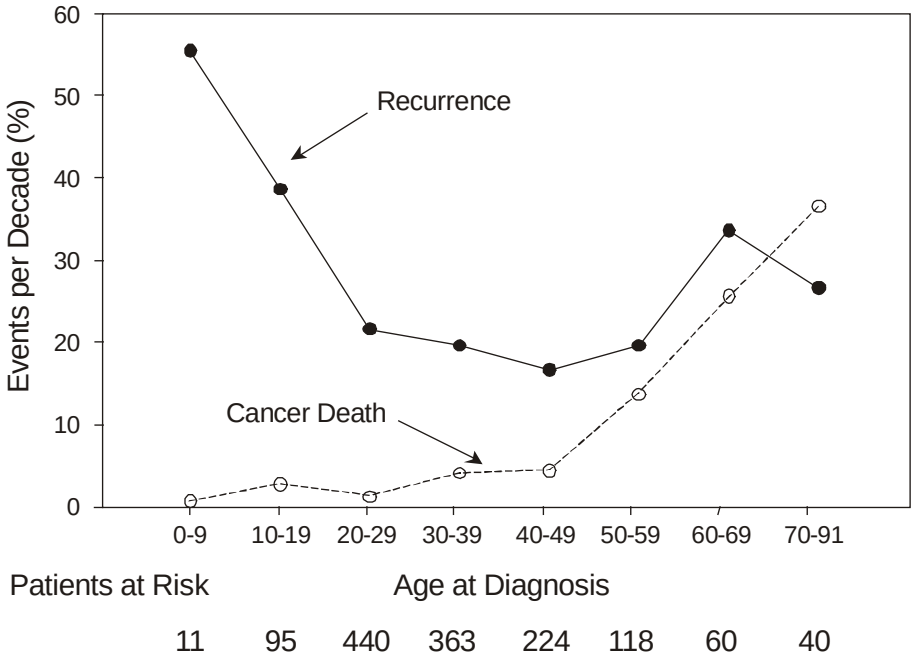

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Figure 2:

Relationship of cancer recurrence and mortality to tumor size

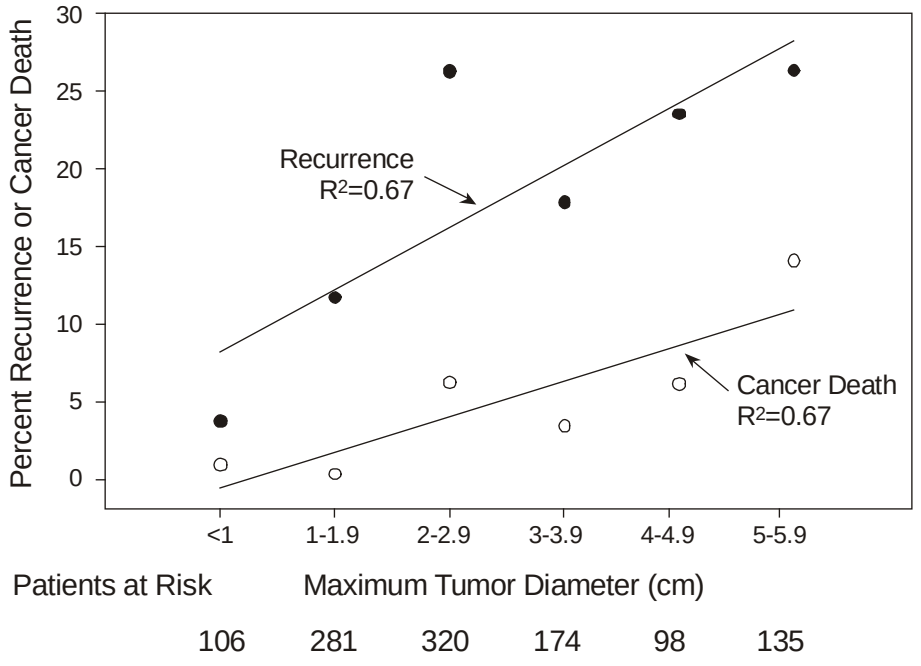

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Table 2

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

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

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