

National Comprehensive
Cancer Network[®]

Thyroid Carcinoma

Version 1.2001

Continue

NCCN Thyroid Carcinoma Panel Members

*Steven I. Sherman, MD/Chair
University of Texas M.D. Anderson Cancer
Center

Samuel W. Beenken, MD
University of Alabama at Birmingham
Comprehensive Cancer Center

Orlo H. Clark, MD
UCSF Comprehensive Cancer Center

Gilbert H. Daniels, MD
Massachusetts General Hospital

Hormoz Ehya, MD
Fox Chase Cancer Center

Robert F. Gagel, MD
University of Texas M.D. Anderson
Cancer Center

Francis S. Greenspan, MD
UCSF Comprehensive Cancer Center

Fouad Kandeel, MD
City of Hope Cancer Center

Richard T. Kloos, MD
Arthur G. James Cancer Hospital &
Richard J. Solove Research Institute
at Ohio State University

Dominick M. Lamonica, MD
Roswell Park Cancer Institute

Thom R. Loree, MD
Roswell Park Cancer Institute

William Lydiatt, MD
UNMC Eppley Cancer Center at the
University of Nebraska Medical Center

Judith McCaffrey, MD
H. Lee Moffitt Cancer Center and Research
Institute at the University of South Florida

Mark E. Molitch, MD
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Marvin L. Rallison, MD
Huntsman Cancer Institute at the
University of Utah

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

Richard Robbins, MD
Memorial Sloan-Kettering Cancer Center

Gary Schwartz, MD
Roswell Park Cancer Institute

Jatin P. Shah, MD
Memorial Sloan-Kettering Cancer Center

James C. Sisson, MD
University of Michigan Comprehensive
Cancer Center

Stewart Spies, MD
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Norman W. Thompson, MD
University of Michigan Comprehensive
Cancer Center

Robert Udelsman, MD
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

* Writing Committee member

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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.

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

See [NCCN Categories of Consensus](#)

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CLINICAL PRESENTATION

WORK-UP

Thyroid
nodule

Clinically suspicious: Nodules > 1 cm in diameter

Increased suspicion if any of the following are present:

- Age < 15 y or > 45 y
- Male sex
- Nodule > 4 cm in diameter
- History of radiation exposure
- History of diseases associated with thyroid cancer:
 - › Pheochromocytoma
 - › Hyperparathyroidism
 - › Gardner’s syndrome
 - › Familial adenomatous polyposis
 - › Carney complex
 - › Cowden’s syndrome

Highly suspicious^a:

- Rapid nodule growth
- Very firm nodule
- Fixation to adjacent structures
- Family history of thyroid cancer
- Vocal cord paralysis
- Enlarged regional lymph nodes
- Symptoms of invasion into neck structures

Clinically euthyroid:

- TSH measurement
- FNA of nodule (consider FNA of clinically suspicious lymph nodes)

[See FNA Results \(THYR-2\)](#)

Clinically nonsuspicious:

Nodules < 1 cm in diameter without enlarged cervical lymph nodes and none of the criteria above

Follow-up as clinically indicated

Papillary carcinoma, incidental finding postthyroidectomy

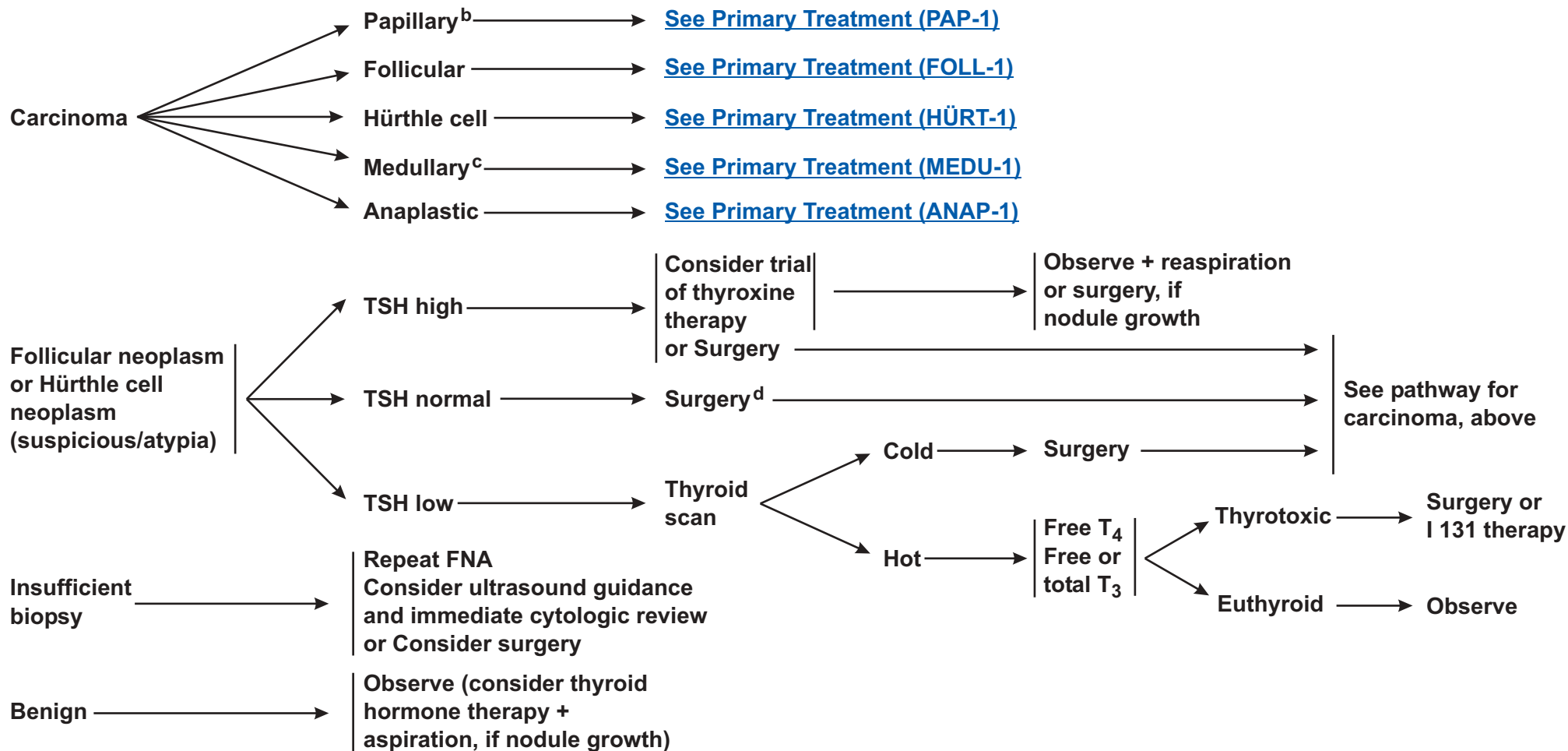
[See Primary Treatment \(PAP-2\)](#)

^aConsider surgery after FNA.

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FNA RESULTS

TREATMENT



^bThis includes cytology suspicious for papillary carcinoma.

^cIf suspicious, perform serum calcitonin and CEA.

^dConsider trial of thyroxine therapy for small clinically nonsuspicious follicular neoplasm.

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FNA FINDING

DIAGNOSTIC
PROCEDURES

PREOPERATIVE OR INTRAOPERATIVE
RISK FACTORS

Papillary carcinoma
FNA positive

- Chest x-ray
- Consider neck ultrasound
- CT/MRI for fixed or substernal lesions (avoid iodinated contrast, unless essential)

- High risk: (any present)
- Age < 15 y or > 45 y
 - Radiation history
 - Known distant metastases
 - Bilateral disease
 - Extrathyroidal extension
 - Tumor > 4 cm in diameter
 - Cervical lymph node metastases

[See Primary Treatment \(PAP-3\)](#)

- Moderate/low risk: (all present)
- Age 15 y - 45 y
 - No prior radiation
 - No distant metastases
 - No cervical lymph node metastases
 - No extrathyroidal extension
 - Tumor < 4 cm in diameter
 - No family history of thyroid cancer

[See Primary Treatment \(PAP-3\)](#)

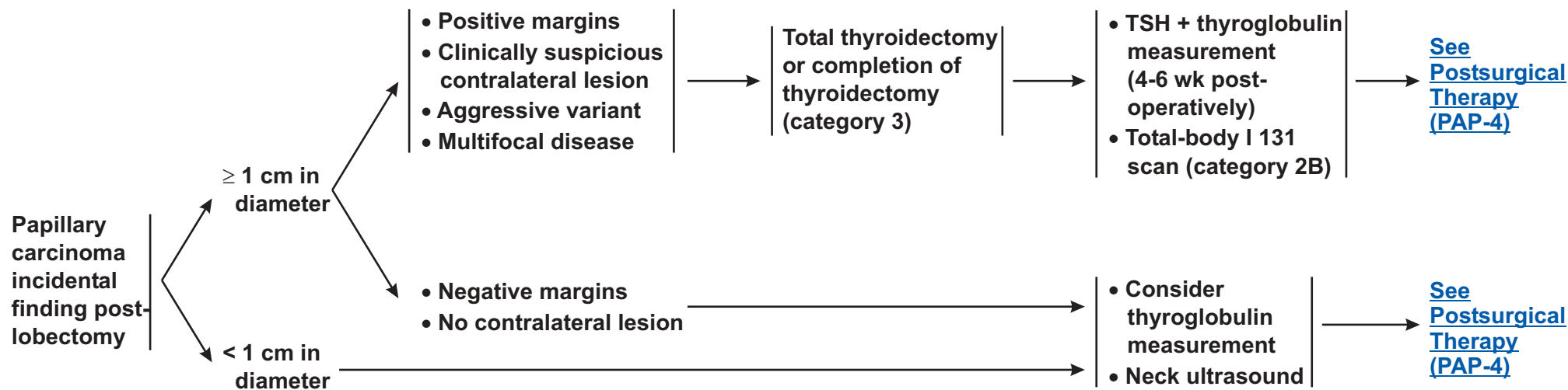
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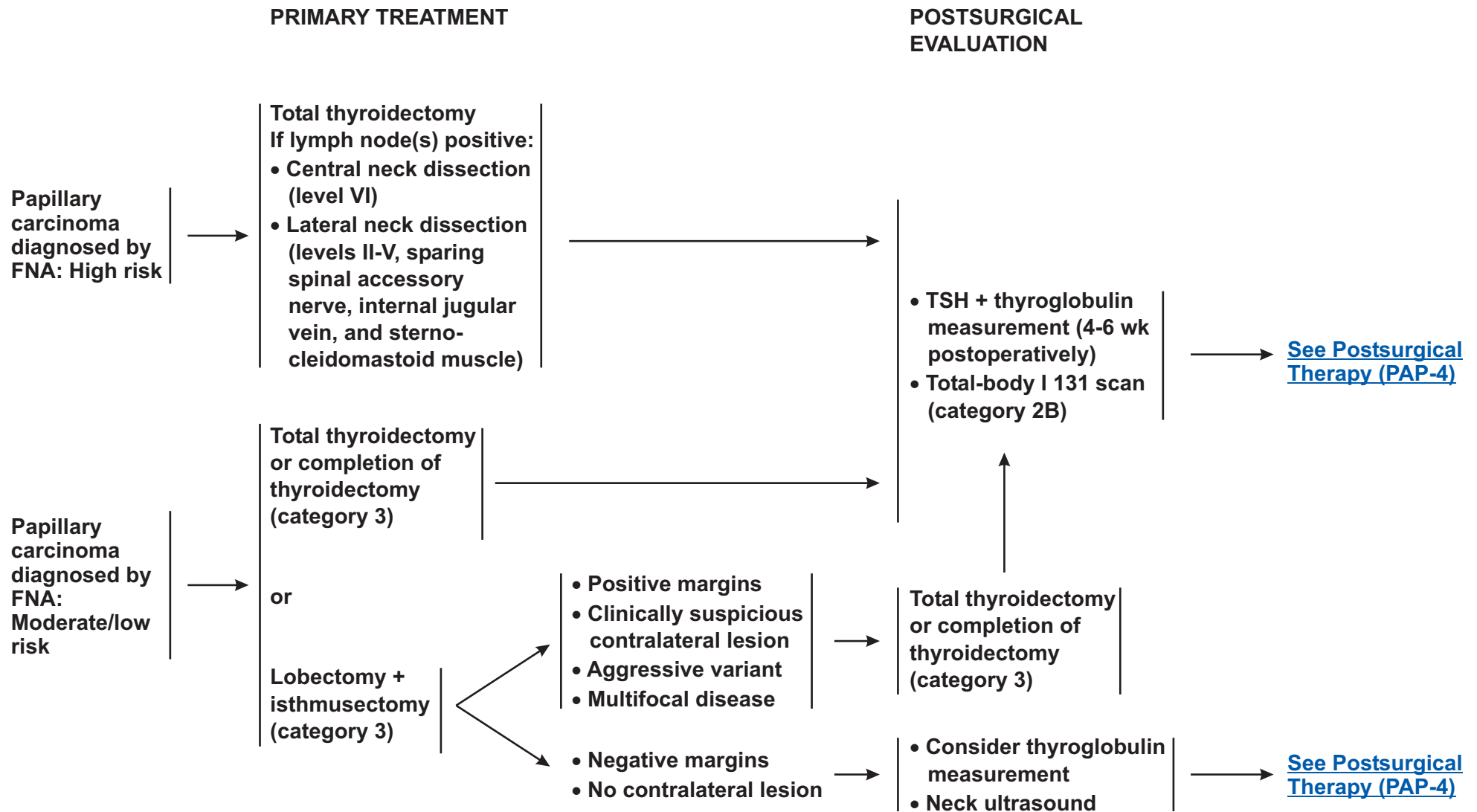
FNA FINDING

PRIMARY TREATMENT

POSTSURGICAL
EVALUATION



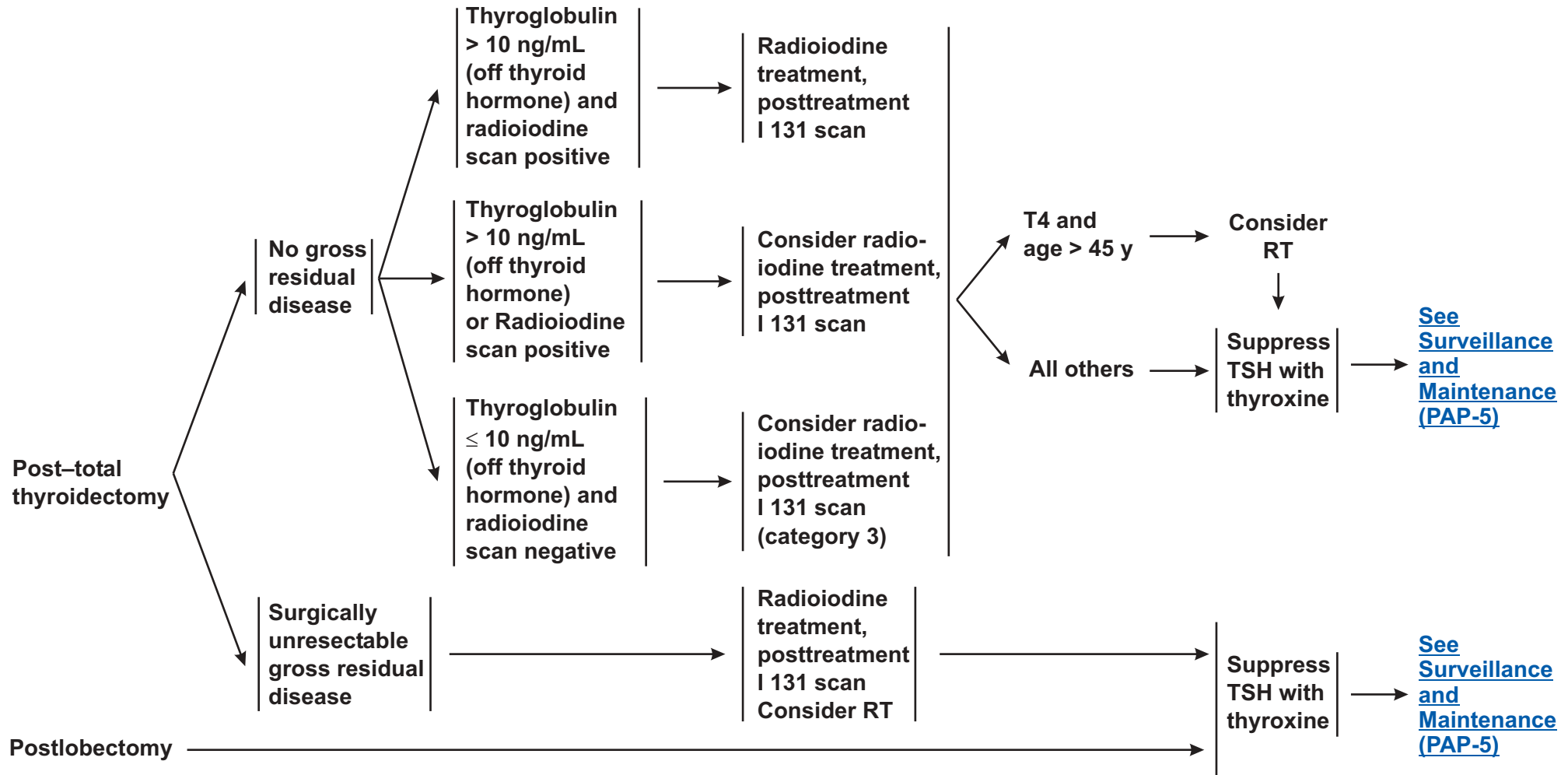
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POSTSURGICAL
EVALUATION

POSTSURGICAL THERAPY

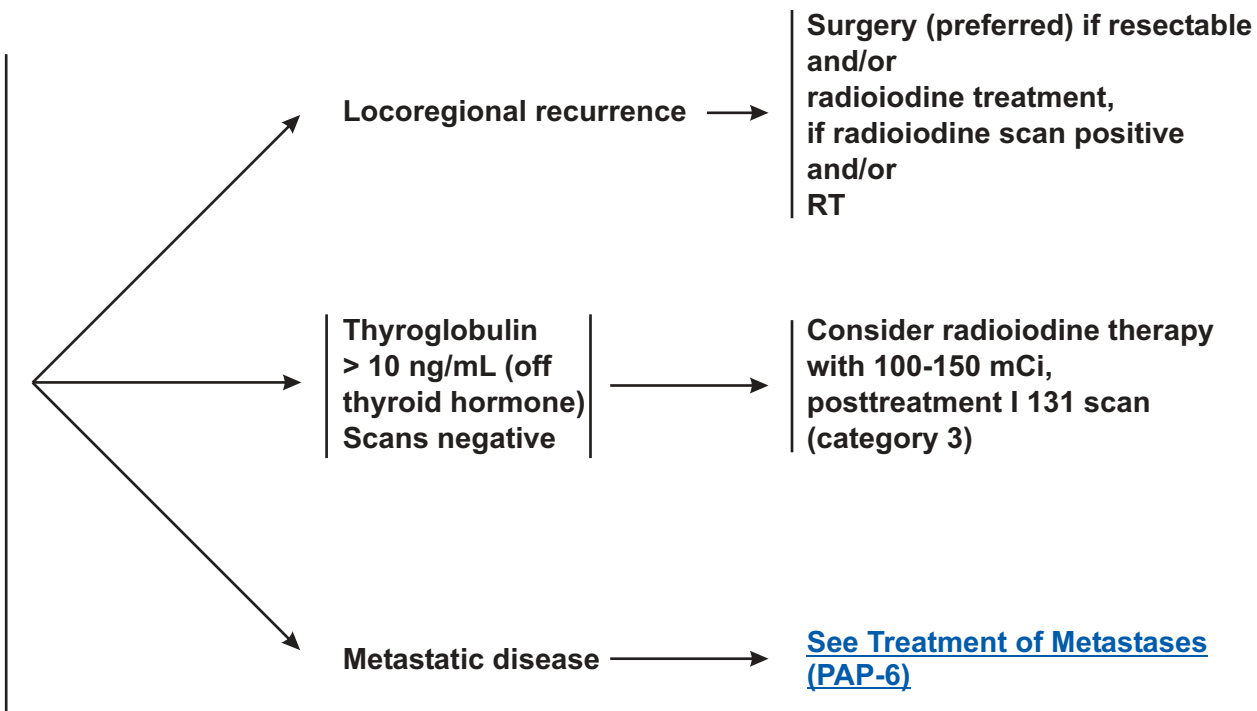


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SURVEILLANCE AND MAINTENANCE

- Physical exam every 3-6 mo for 2 y, then annually if disease-free
- Thyroglobulin measurement at 6 and 12 mo, then annually if disease-free
- Radioiodine scan every 12 mo until 1 or 2 negative scans (withdrawal of either thyroid hormone or rhTSH) if total thyroidectomy and ablation
- Consider periodic neck ultrasound and chest x-ray
- Consider additional nonradioiodine imaging, if I 131 scans negative and serum thyroglobulin elevated > 10 ng/mL, on or off thyroxine therapy, or > 5 ng/mL after rhTSH

RECURRENT DISEASE



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TREATMENT OF METASTASES

Solitary CNS	→	Consider neurosurgical resection and/or radioiodine treatment with rhTSH and steroid prophylaxis, if radioiodine scan positive and/or RT
Bone	→	Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities and/or radioiodine treatment, if radioiodine scan positive and/or RT
Disseminated	→	Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing or Systemic chemotherapy, consider clinical trials for non-iodide-concentrating tumors

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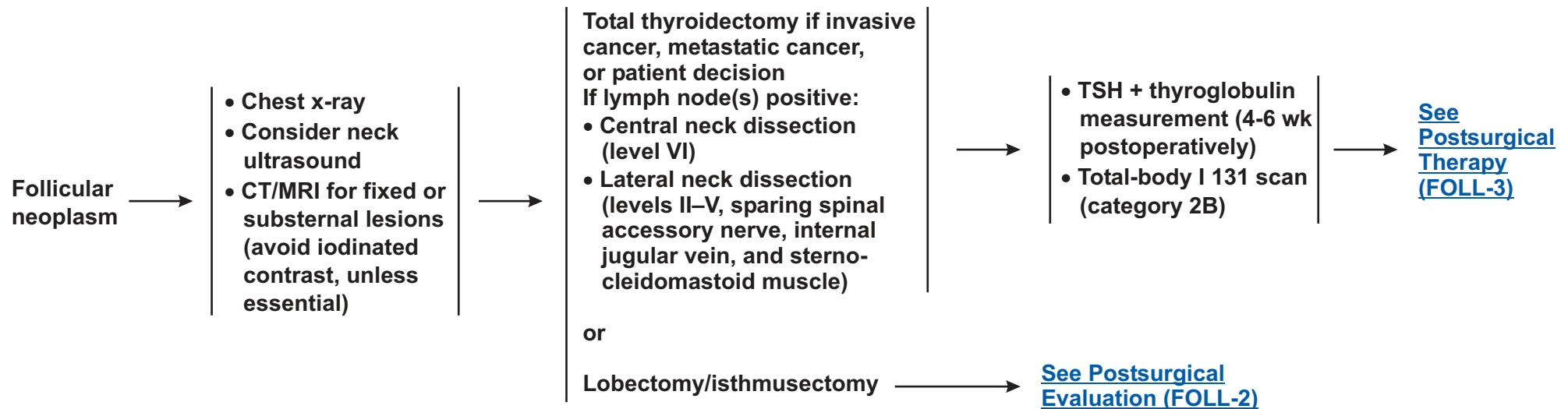
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FNA FINDING

DIAGNOSTIC PROCEDURES

PRIMARY TREATMENT

POSTSURGICAL EVALUATION

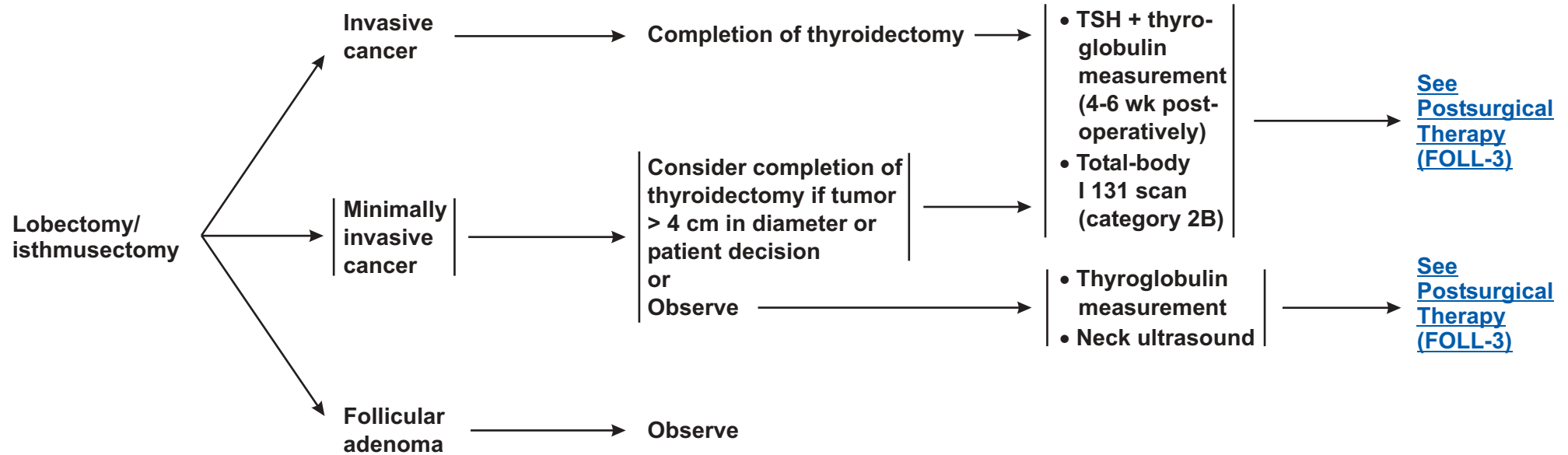


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PRIMARY TREATMENT

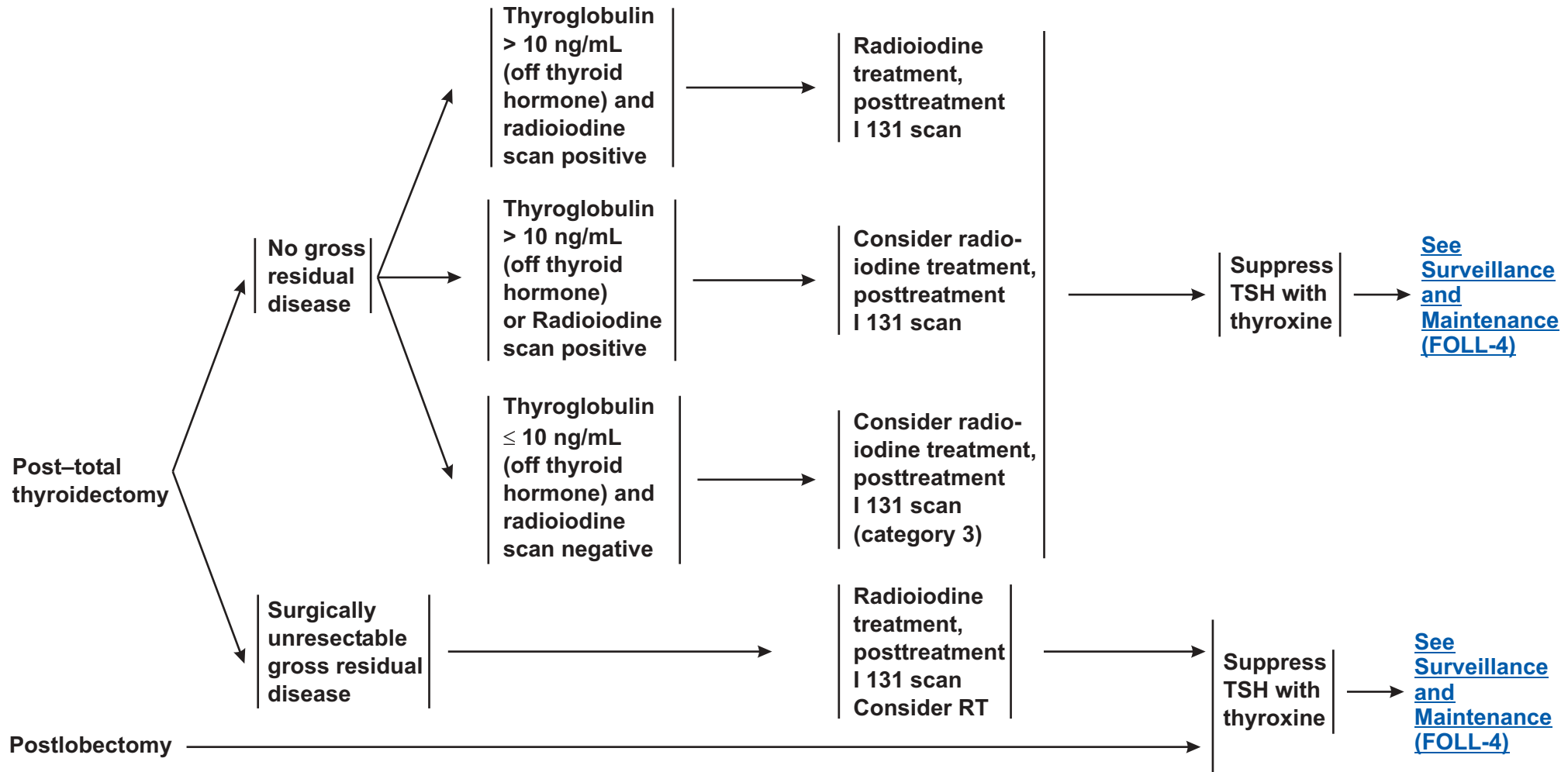
POSTSURGICAL EVALUATION



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**POSTSURGICAL
EVALUATION**

POSTSURGICAL THERAPY

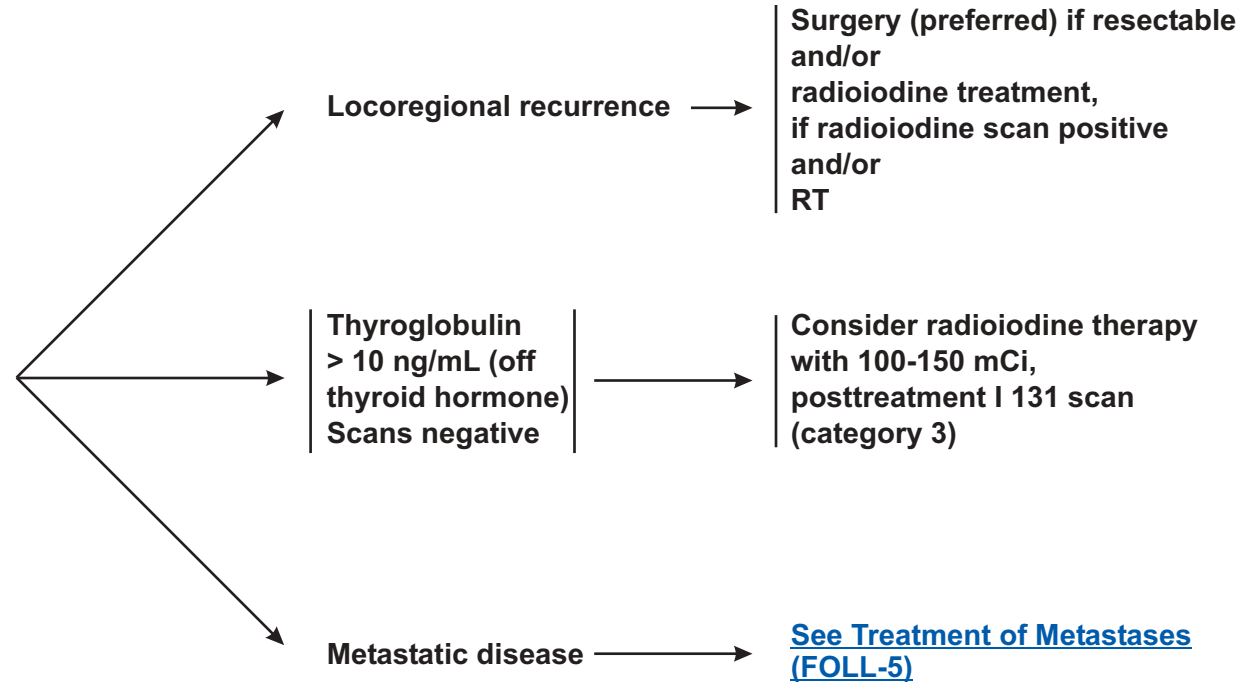


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SURVEILLANCE AND MAINTENANCE

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- Thyroglobulin measurement at 6 and 12 mo, then annually if disease-free
- Radioiodine scan every 12 mo until 1 or 2 negative scans (withdrawal of either thyroid hormone or rhTSH) if total thyroidectomy and ablation
- Consider periodic chest x-ray
- Consider additional nonradioiodine imaging, if I 131 scans negative and serum thyroglobulin elevated > 10 ng/mL, on or off thyroxine therapy, or > 5 ng/mL after rhTSH

RECURRENT DISEASE



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TREATMENT OF METASTASES

Solitary CNS	→	Consider neurosurgical resection and/or radioiodine treatment with rhTSH and steroid prophylaxis, if radioiodine scan positive and/or RT
Bone	→	Surgical palliation, if symptomatic or asymptomatic in weight-bearing extremities and/or radioiodine treatment, if radioiodine scan positive and/or RT Consider biphosphate (pamidronate) for symptomatic metastases (category 2B)
Disseminated	→	Radioiodine if positive uptake, with consideration of dosimetry to maximize dosing or Systemic chemotherapy, consider clinical trials for non-iodide-concentrating tumors

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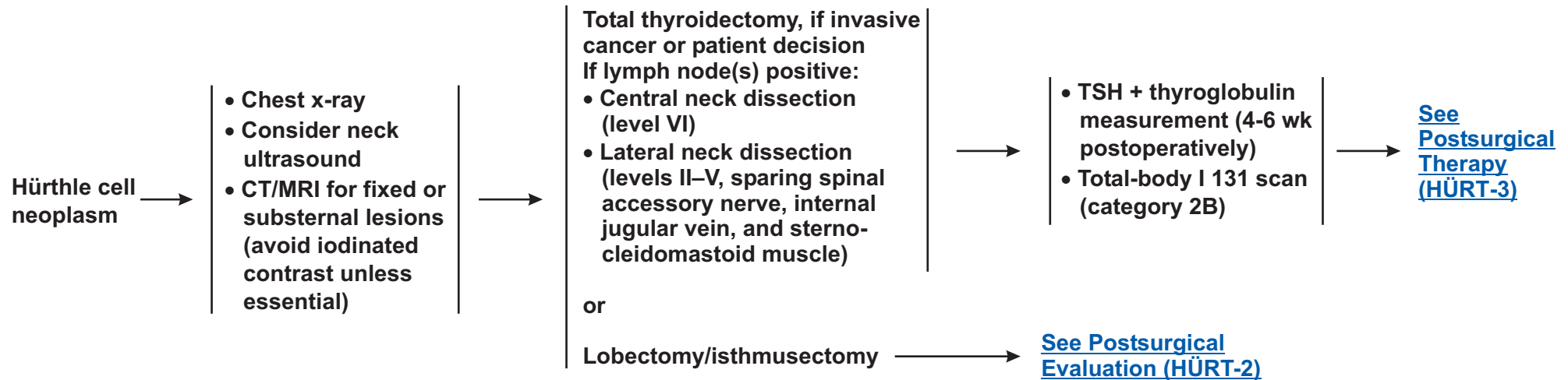
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FNA FINDING

DIAGNOSTIC
PROCEDURES

PRIMARY TREATMENT

POSTSURGICAL EVALUATION

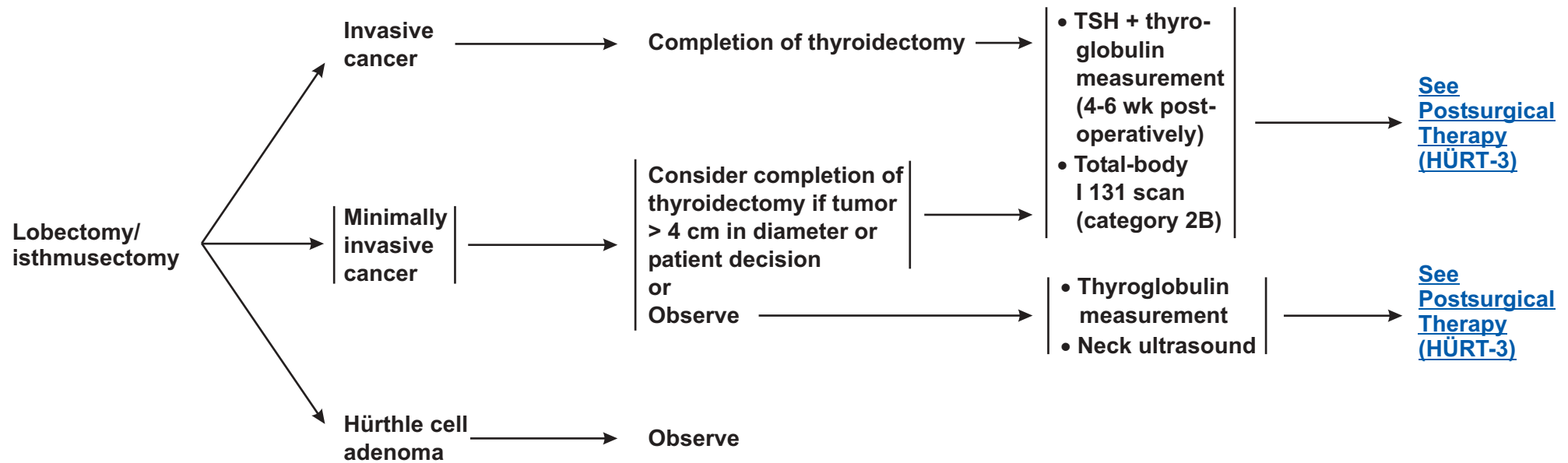


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PRIMARY TREATMENT

POSTSURGICAL EVALUATION



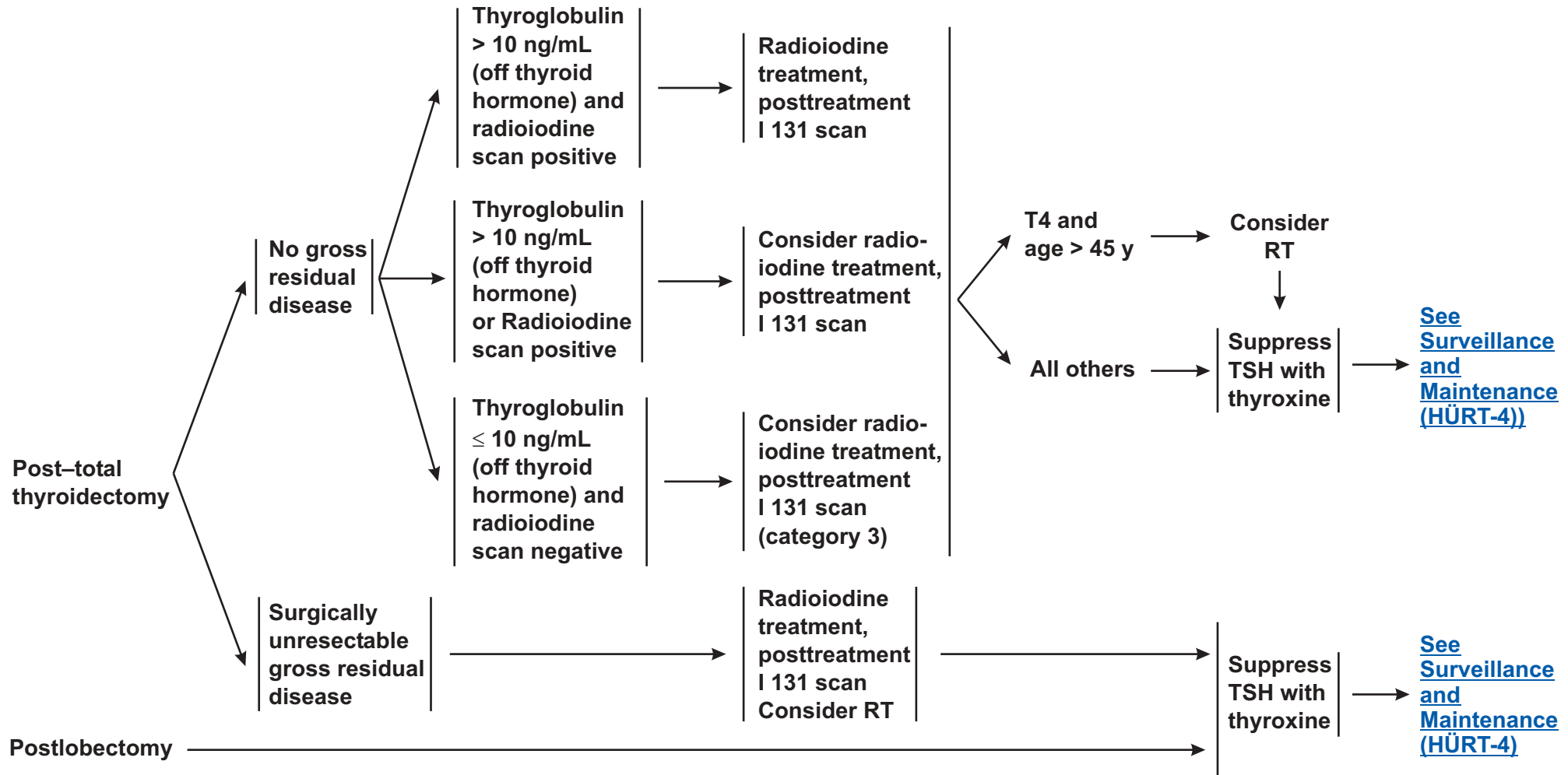
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HÜRT-2

**POSTSURGICAL
EVALUATION**

POSTSURGICAL THERAPY

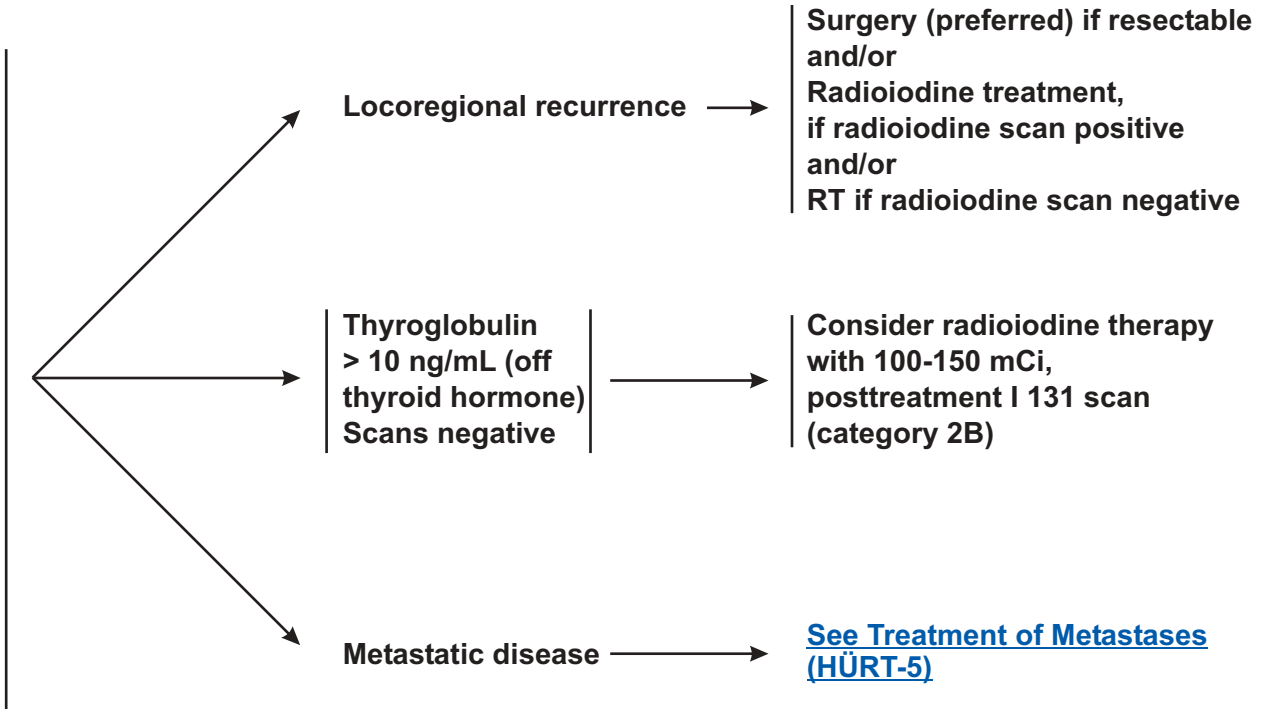


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SURVEILLANCE AND MAINTENANCE

- Physical exam every 3-6 mo for 2 y, then annually if disease-free
- Thyroglobulin measurement at 6 and 12 mo, then annually if disease-free
- Radioiodine scan every 12 mo until 1 or 2 negative scans (withdrawal of either thyroid hormone or rhTSH) if total thyroidectomy and ablation
- Consider periodic neck ultrasound and chest x-ray
- Consider additional nonradioiodine imaging, if I 131 scans negative and serum thyroglobulin elevated > 10 ng/mL, on or off thyroxine therapy, or > 5 ng/mL after rhTSH

RECURRENT DISEASE



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TREATMENT OF METASTASES

Solitary CNS	→	Consider neurosurgical resection and/or RT
Bone	→	Surgical resection, if symptomatic or asymptomatic in weight-bearing extremities and/or RT
Disseminated	→	Radioiodine, if positive uptake, with consideration of dosimetry to maximize dosing or Systemic chemotherapy, consider clinical trials for non-iodide-concentrating tumors

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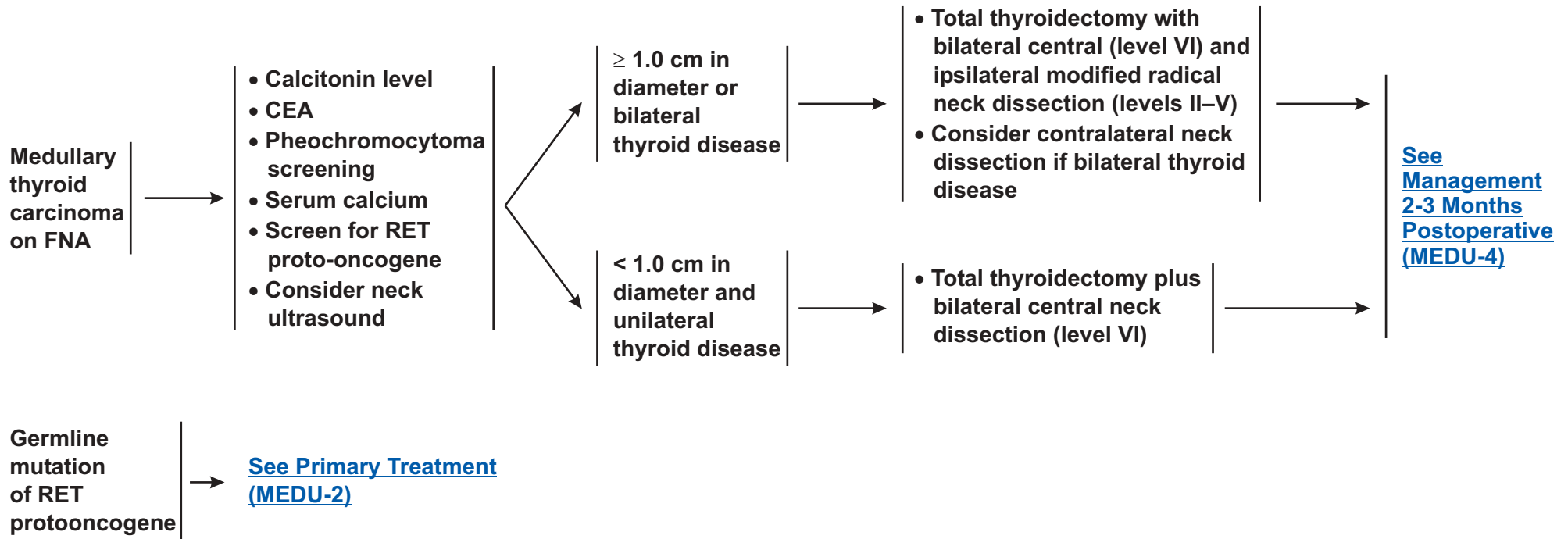
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

HÜRT-5

CLINICAL PRESENTATION

ADDITIONAL WORK-UP

PRIMARY TREATMENT



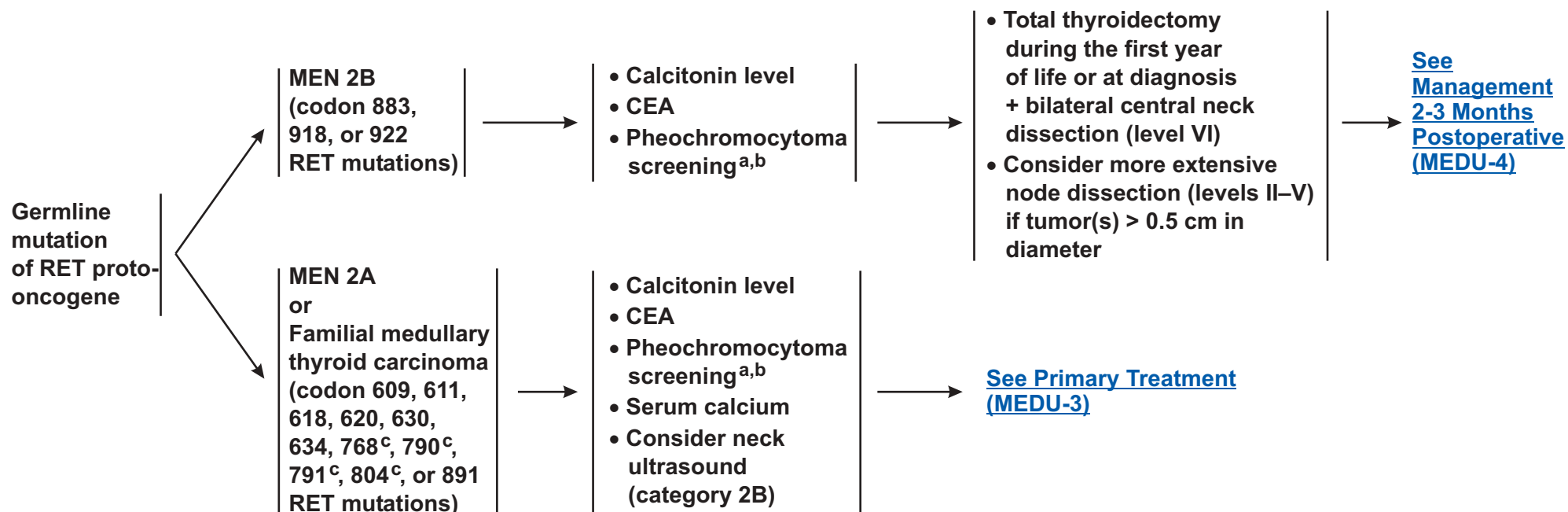
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CLINICAL
PRESENTATION

ADDITIONAL WORK-UP

PRIMARY TREATMENT



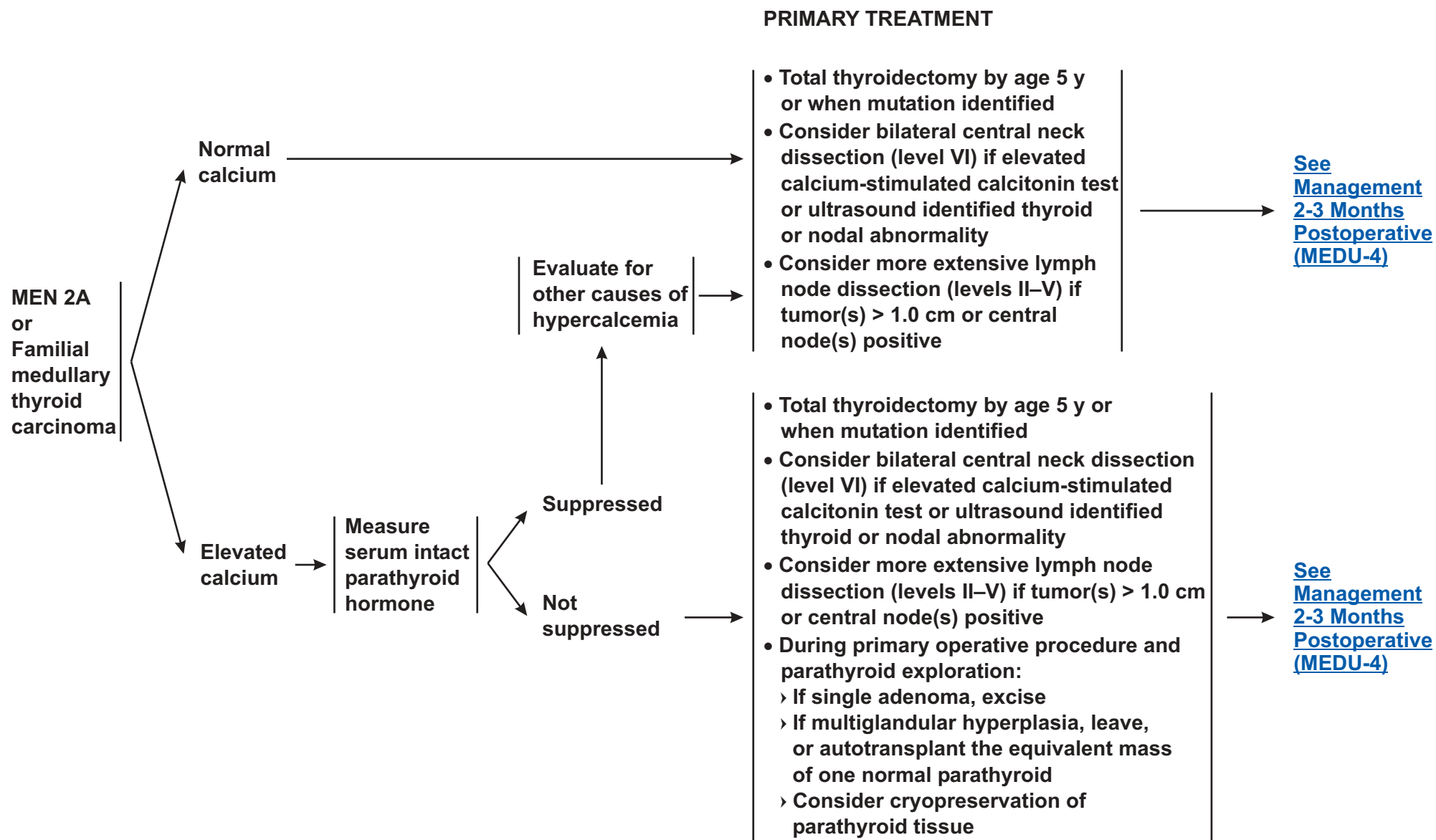
^aEvidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.

^bScreening for pheochromocytoma and hyperparathyroidism should be performed annually.

^cVirulence 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 or pentagastrin) calcitonin testing may be continued, with total thyroidectomy and central node dissection deferred until tests become abnormal after the age of 5 years.

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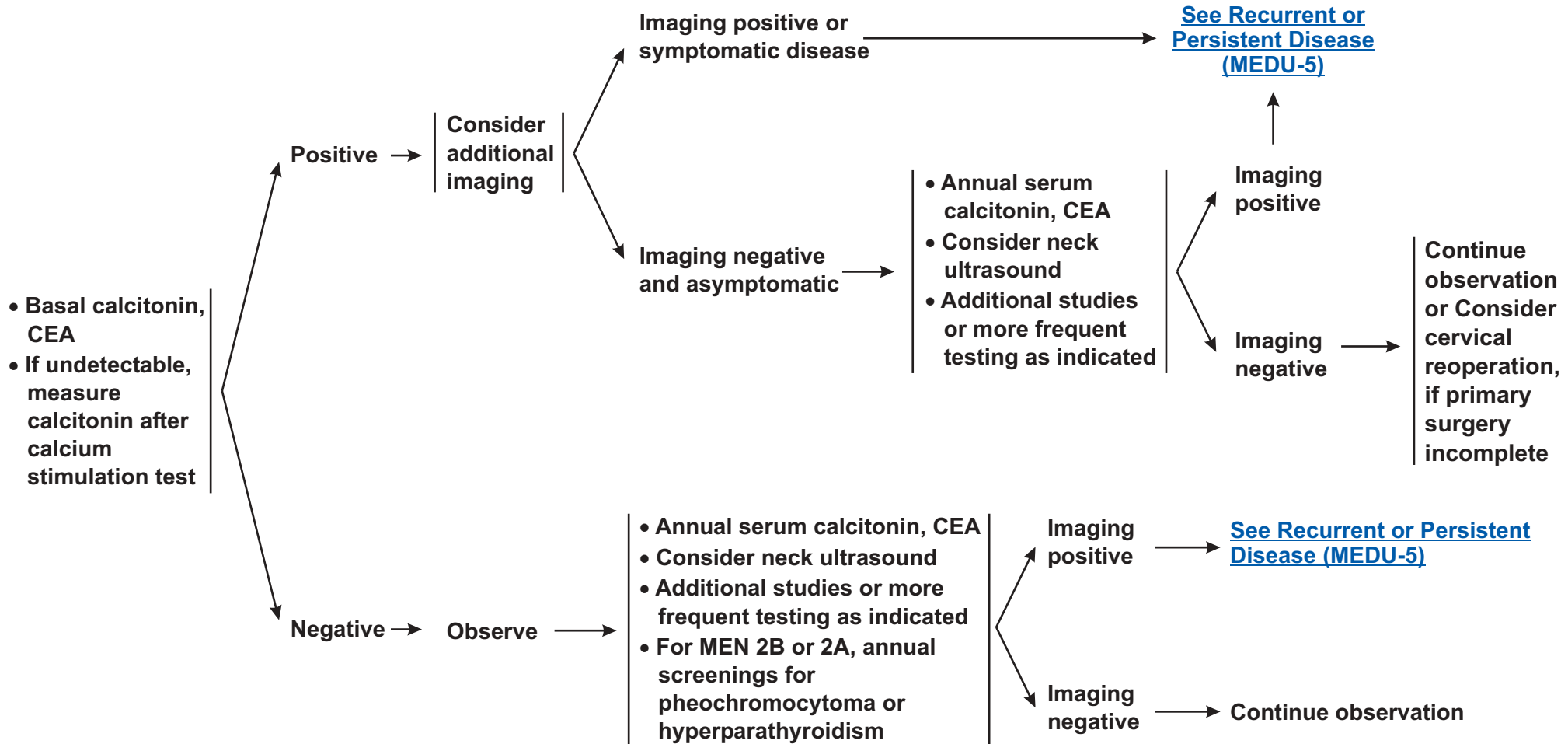


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MANAGEMENT
2-3 MONTHS
POSTOPERATIVE

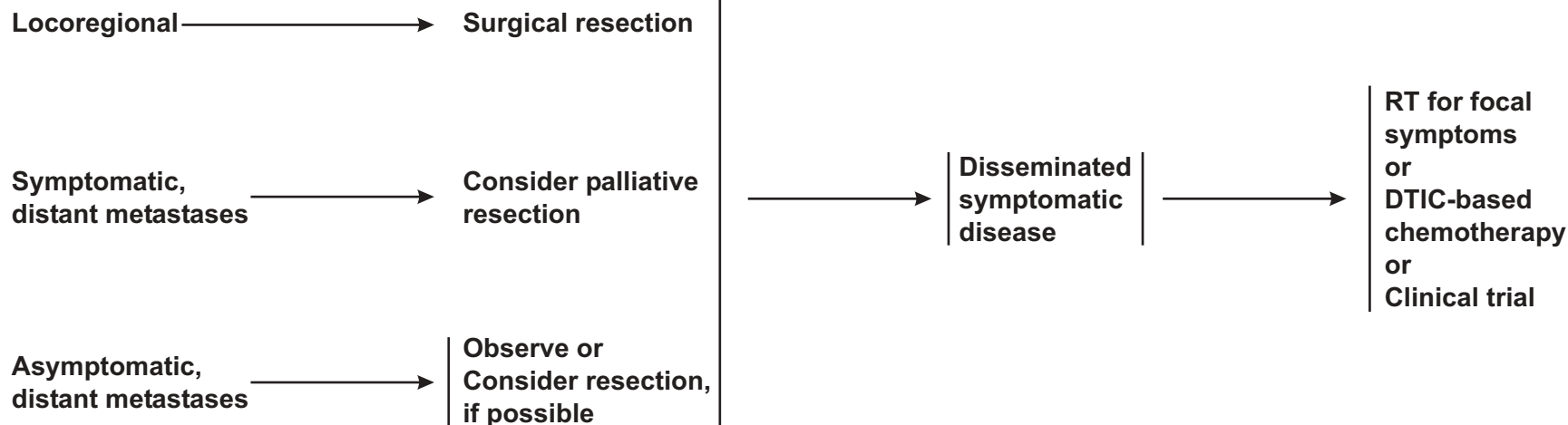
SURVEILLANCE



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RECURRENT OR PERSISTENT DISEASE



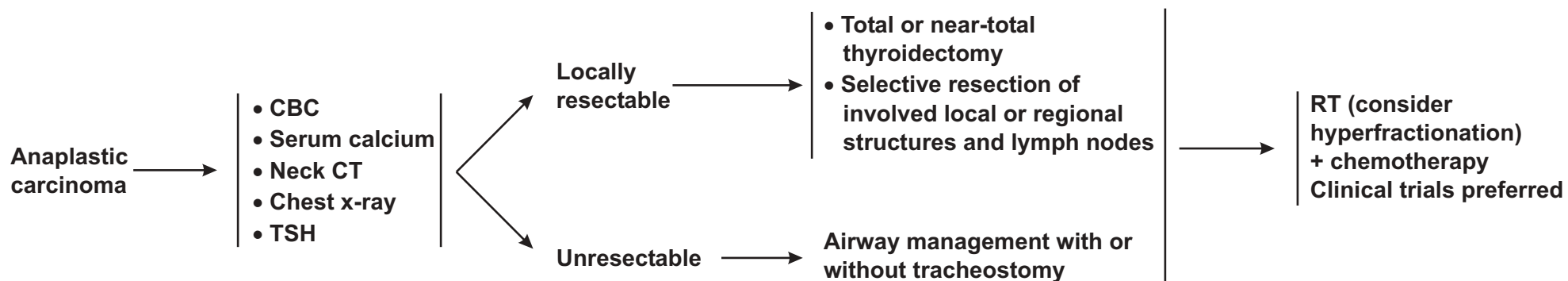
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FNA OR CORE
BIOPSY FINDING

DIAGNOSTIC
PROCEDURES

PRIMARY TREATMENT



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Staging

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 1 cm or less in greatest dimension limited to the thyroid
- T2** Tumor more than 1 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
- T4** Tumor of any size extending beyond the thyroid capsule

Regional Lymph Nodes (N)

Regional lymph nodes are the 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 in ipsilateral cervical lymph node(s)
 - N1b** Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)

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, follicular, medullary, or undifferentiated (anaplastic).

Papillary or Follicular

	UNDER 45 YEARS	45 YEARS AND OLDER
Stage I	Any T, Any N, M0	T1, N0, M0
Stage II	Any T, Any N, M1	T2, N0, M0 T3, N0, M0
Stage III		T4, N0, M0 Any T, N1, M0
Stage IV		Any T, Any N, M1

Medullary

Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
	T4	N0	M0
Stage III	Any T	N1	M0
Stage IV	Any T	Any N	M1

Undifferentiated (anaplastic)

All cases are Stage IV

Stage IV	Any T	Any N	Any M
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Manuscript

NCCN Categories of Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

This article summarizes the Thyroid Carcinoma Practice Guidelines of the National Comprehensive Cancer Network (NCCN). As background to this discussion, an overview of the epidemiology, etiology, histology, prognostic factors, and the staging and treatment of thyroid cancer is provided.

Epidemiology of Thyroid Carcinoma

Thyroid nodules are about fourfold more common in women than men. These nodules increase in frequency throughout life, reaching a prevalence of about 5% in the US population aged 50 years and older (Mazzaferri, 1993a). Nodules are even more prevalent when the gland is examined at autopsy, at surgery or by ultrasonography.

Half the thyroids so studied have nodules, which are almost always benign (Mazzaferri, 1993a; Ezzat et al, 1994). New nodules develop at a rate of about 0.1% per year, beginning in early life, but develop at a much higher rate--about 2% per year--following exposure to head and neck irradiation (Ron et al, 1995; Schneider et al, 1997).

By contrast, thyroid carcinoma is uncommon. Approximately 19,500 new cases of thyroid carcinoma will be diagnosed in the United States in the year 2001 (Greenlee et al, 2001). This cancer occurs two to three times as often in women as in men and more often in whites than in African-Americans. Although thyroid carcinoma occurs at all ages, the peak incidence is around 40 years of age in women and at 60 years of age in men (Kosary et al, 1995).

For the US population, the lifetime risk of being diagnosed with thyroid carcinoma is about 1% (0.65% for women and 0.25% for men) (Kosary et al, 1995). Information from the National Cancer Data Base (NCDB) indicates 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 (Hundahl et al, 1998).

In 2001, there will be approximately 1,300 cancer deaths among an estimated 135,000 persons living with thyroid carcinoma in the United States (Greenlee et al, 2001). Although thyroid carcinoma occurs more often in women, mortality rates are higher in men, probably because they are older than women at the time of diagnosis (Mazzaferri and Jhiang, 1994; Kosary et al, 1995).

The incidence of thyroid carcinoma rose steadily between 1973 and 1992--almost 28%--while its mortality rates dropped more than 23% (Kosary et al, 1995). Although the causes of these statistically

significant changes are uncertain, the rising incidence may be due to the increase in radiation-induced thyroid carcinoma (Ron et al, 1995). The decline in mortality is likely due to therapy for differentiated thyroid carcinoma detected at an early stage when it is most amenable to surgery and radioactive iodine 131 (I 131) (Mazzaferri and Jhiang, 1994).

The Challenge of Managing Differentiated Thyroid Carcinoma

The management of differentiated (papillary and follicular) thyroid carcinoma is a challenge because there have been no prospective randomized trials of treatment. Results from those randomized trials under consideration will not be available for many years given the typically prolonged course and relative infrequency of these tumors. Accordingly, most of the information about treatment comes from studies of large patient cohorts in which therapy has not been randomized and accounts for much of the disagreement about management.

Nonetheless, most patients can be cured of this disease when properly managed by experienced physicians and surgeons. The treatment of choice is surgery, whenever possible, followed in most patients by I 131 and thyroxine therapy. External radiation and chemotherapy have a less prominent role in the management of these tumors.

Radiation-Induced Thyroid Carcinoma

Exposure to ionizing radiation is the only known environmental cause of thyroid carcinoma, usually 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 and the only organ linked by convincing evidence of having risk at about

0.10 Gy (Ron et al, 1995).

The risk is greater for females, for certain Jewish populations, and patients with a family history of thyroid carcinoma (Wong et al, 1996), reflecting the importance of genetics 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 (Ron et al, 1995; Schneider et al, 1997).

Until recently, most studies showed that I 131 is less effective than external gamma radiation in inducing thyroid carcinoma (Hall and Holm, 1998). However, most of the studies that came to this conclusion were of adults in whom the risk of developing thyroid carcinoma after exposure to I 131 appears to be small or nonexistent (Ron et al, 1998). After the Chernobyl nuclear reactor accident in 1986, a large number of children developed papillary thyroid carcinoma after being exposed to radioiodine fallout. It became evident that I 131 and other short-lived radioiodines were potent thyroid carcinogens in children, particularly those exposed under the age of 10 years (Jacob et al, 1998). Although there is a tendency for radiation-induced papillary thyroid cancer 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 (Schneider, 1990; Nikiforov et al, 1998).

Diagnosis of Thyroid Carcinoma

Clinical Presentation: Differentiated thyroid carcinoma is usually asymptomatic for long periods and usually presents as a solitary thyroid nodule. The evaluation for malignancy is difficult, however, because benign nodules are so prevalent and thyroid carcinoma, by

contrast, is so uncommon (Mazzaferri, 1993a). Moreover, both benign and malignant thyroid nodules are usually asymptomatic, giving no clinical clue to their cause.

About half the malignant nodules come to attention during a routine physical examination or by serendipity on imaging studies or during surgery for benign disease. The other half are usually first noticed by the patient, usually as an asymptomatic nodule (Mazzaferri, 1993a). 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 (Mazzaferri and Jhiang, 1994).

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 (Mazzaferri, 1993a; Ezzat et al, 1994; Tan and Gharib, 1997). By contrast, nodules over 4 cm in diameter are more suspicious and pose a somewhat higher risk of malignancy.

Although over half of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule rises considerably when signs or symptoms are present (Mazzaferri, 1992). For example, the likelihood that a nodule is malignant increases about sevenfold if it is a very firm nodule, fixed to adjacent structures, associated with enlarged regional lymph nodes, causes vocal cord paralysis, is rapidly growing, or symptoms of invasion into neck structures are present (Hamming et al, 1990; Mazzaferri, 1992). If

two or more of these features are present, the likelihood of thyroid cancer is virtually assured (Hamming et al, 1990).

Likewise, a patient's age has a bearing on the probability of malignancy. The risk of malignancy is higher in patients under 15 years of age and over 60 years of age, especially older men. A man over 60 years of age with a thyroid nodule has about four times the risk of having thyroid carcinoma than does a middle-aged woman with a thyroid nodule (Belfiore et al, 1992).

Other factors that raise the suspicion of malignancy include: (1) a past history of head and neck irradiation, (2) a family history of thyroid carcinoma, (3) the presence of certain familial syndromes associated with thyroid carcinoma (described under the heading “Familial Syndromes Linked to Papillary Thyroid Cancer,” below), or (4) evidence of other diseases associated with the multiple endocrine neoplasia type 2 syndromes (MEN 2), such as hyperparathyroidism, pheochromocytoma, a marfanoid habitus, or mucosal neuromas (MEN 2B).

Initial Work-up: Fine needle aspiration (FNA) of the nodule or clinically suspicious lymph nodes is recommended as the first diagnostic test in a clinically euthyroid patient before any imaging studies are done (Mazzaferri, 1993a). Ideally, the serum thyrotropin (TSH) results should be known before FNA is performed. This is often impractical and FNA may be done during the initial office visit. Some clinicians, especially European thyroidologists (Henry et al, 1996), recommend obtaining serum calcitonin levels from all patients with thyroid nodules, but this practice is not very cost effective and has not been recommended by the American Thyroid Association (Singer et al, 1996).

Fine needle aspiration cytology results are usually categorized as carcinoma, follicular, or Hürthle cell neoplasm (suspicious or indeterminate), insufficient biopsy, or benign. Fine needle aspiration that yields insufficient cytology for diagnosis should be repeated because approximately half of the repeat specimens are adequate for diagnosis (Mazzaferri, 1992). In patients with repeated nondiagnostic aspirates, 5% of women and 30% of men may prove to have malignant nodules (McHenry et al, 1993). Nodules that yield an abundance of follicular cells with little or no colloid are nearly impossible to categorize as benign or malignant. These particular nodules often require surgery because about 20% of them are minimally invasive follicular carcinomas (Mazzaferri, 1992). Repeat FNA is not generally recommended because it will not solve the diagnostic dilemma.

Before thyroidectomy is performed, however, the serum TSH level and thyroid ¹²³I or ^{99m}Tc scanning can identify patients with a hot nodule who can be spared surgery (Cersosimo et al, 1993). Euthyroid patients with a low TSH and a “hot” nodule on thyroid scan may be observed. Those with a hot nodule on thyroid scan who are found to be thyrotoxic may be treated with surgery or I 131 therapy. Those patients with a high TSH whose cytology is suspicious for follicular or Hurthle cell neoplasm may be treated by a trial of thyroxine therapy or surgery. If the patient receives thyroxine therapy, reaspiration or surgery may be considered in the event of nodule growth. Those individuals with a normal TSH should proceed with surgery. Nodules yielding benign cytology do not require repeat FNA unless the nodules show evidence of growth (Mazzaferri, 1992). Controversy continues about the use of thyroid hormone therapy for benign thyroid nodules (Gharib and Mazzaferri, 1998; Ridgway, 1998).

When a diagnosis of thyroid carcinoma is established promptly by FNA, the tumor is often confined to the thyroid or has metastasized only to regional nodes, thus providing ample opportunity for cure. Regardless, at the time of diagnosis, as many as 5% of patients with papillary carcinoma, and up to 10% of those patients with follicular or Hürthle cell carcinoma, have tumors which aggressively invade the neck or have produced distant metastases, drastically lowering the likelihood of a cure.

Prognosis and Recurrence

In the NCDB study, 10 year relative survival rates with papillary, follicular, and Hürthle cell carcinomas were 93%, 85%, and 76%, respectively (Hundahl et al, 1998). Although anaplastic thyroid carcinoma is uniformly lethal, most of the thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases.

Depending upon the initial therapy and other prognostic variables, about 30% of patients with differentiated thyroid carcinoma have tumor recurrences over several decades, two thirds of which occur within the first decade after initial therapy (Mazzaferri and Jhiang, 1994). Although not usually fatal, a recurrence in the neck is a serious event that must be regarded as the first sign of a potentially lethal outcome (Newman et al, 1998; Robie et al, 1998).

In one large study, local recurrences were seen most often in the cervical lymph nodes (74%), followed by the thyroid remnant (20%) and the trachea or muscle (6%). Of the group with local recurrences, 8% died of cancer (Mazzaferri and Jhiang, 1994). Distant metastases were the site of recurrence in 21% of this patient cohort, most often (63%) in the lungs alone. Half of these patients with distant metastases died of cancer (Mazzaferri and Jhiang, 1994).

Age and Stage at Diagnosis: While many factors influence the outcome for patients with papillary and follicular thyroid carcinomas, the two most important and consistently demonstrable, are patient age (here and elsewhere, age refers to patient age at the time of initial therapy) and tumor stage (Mazzaferri and Jhiang, 1994; Gilliland et al, 1997; Sherman et al, 1998; Tsang et al, 1998).

Practically every study shows that age is an important prognostic variable predicting cancer mortality. Thyroid carcinoma is more lethal after age 40 years, increasing in severity thereafter with each subsequent decade of life and rising dramatically after age 60 years ([Figure 1](#)).

A remarkably different age pattern, however, emerges with tumor recurrence rates. Rates are highest (40%) at the extremes of life, before 20 years of age and after 60 years of age, and are about half this at other times (Mazzaferri, 1993b; Mazzaferri and Jhiang, 1994; Gilliland et al, 1997; Sherman et al, 1998; Tsang et al, 1998). This single fact accounts for most of the disagreement among clinicians concerning optimal initial surgery. How clinicians weigh the importance of tumor recurrence accounts for the debate over how age should alter the treatment plan, especially for children and young adults.

Children typically present with more advanced disease than adults and have more tumor recurrences after therapy, yet their prognosis for survival is good (Dottorini et al, 1997; Samuel et al, 1998). One study found, however, despite the favorable prognosis for long-term survival of children with thyroid carcinoma (90% at 20 years), the standardized mortality ratio was eightfold higher than predicted (Schlumberger et al, 1987).

Still, some authors believe that a patient's young age imparts such a favorable influence upon survival that it overshadows the prognosis expected from the characteristics of the tumor, thus classifying most thyroid tumors as low risk tumors which may be treated with lobectomy alone (Hay et al, 1993; Shaha et al, 1995; Cady, 1998). Most of those treating the disease, however, believe that the stage of the tumor and its histologic features are as important as the patient's age in determining prognosis and management (DeGroot et al, 1994; Mazzaferri and Jhiang, 1994; Dottorini et al, 1997; Miccoli et al, 1998).

Patient Gender: Prognosis is less favorable in men than in women, but the difference is usually small (Mazzaferri and Jhiang, 1994; Cady, 1998). One study found that gender was an independent prognostic variable for survival and the risk of death from cancer was about twice as high in men as in women (Mazzaferri and Jhiang, 1994). Because of this, men with thyroid carcinoma, especially those who are over 50 years of age, should be regarded with special concern.

Familial Syndromes: Familial, nonmedullary thyroid carcinoma, which accounts for about 5% of papillary carcinomas, may sometimes be clinically more aggressive than the sporadic form (Frankenthaler et al, 1990). 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 (Agostini et al, 1990). Other familial syndromes associated with papillary thyroid carcinoma are Gardner's syndrome, familial adenomatous polyposis, (Soravia et al, 1999), Carney complex (multiple neoplasia and lentiginosis syndrome which affects endocrine glands)

(Stratakis et al, 1997), and Cowden's syndrome (multiple hamartomas) (Marsh et al, 1998). The prognosis for all of these syndromes is not different from the prognosis of spontaneously occurring papillary thyroid carcinoma.

Tumor Variables Affecting Prognosis

Certain tumor features have a profound effect on prognosis (Mazzaferri, 1987; LiVolsi, 1990a; LiVolsi, 1990b; Mazzaferri, 1993b). Perhaps the most important features are tumor histology, primary tumor size, local invasion, and metastases.

Histology: Although survival with typical papillary carcinoma is quite good, cancer-specific mortality rates vary considerably with certain histologic subsets of tumors (Mazzaferri, 1993a). A well-defined tumor capsule, found in about 10% of papillary thyroid carcinomas, is a particularly favorable prognostic indicator. A graver prognosis is associated with (1) anaplastic tumor transformation and tall-cell papillary variants, which have up to a 25% 10-year mortality, (2) columnar variant papillary carcinoma, a rapidly growing tumor with a 90% mortality rate, and (3) diffuse sclerosing variants, which infiltrate the entire gland (LiVolsi, 1995). 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 more common pure papillary lesions (Mazzaferri, 1993b; Tielens et al, 1994; LiVolsi, 1995).

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 having a worse prognosis than capsular penetration alone (van Heerden et al, 1992). Many follicular carcinomas are minimally invasive tumors, exhibiting only slight tumor capsular penetration

without vascular invasion. They closely resemble follicular adenomas and are less likely to produce distant metastases or cause death (LiVolsi and Asa, 1994).

Fine needle aspiration or frozen section study cannot differentiate a minimally invasive follicular carcinoma from a follicular adenoma. The tumor is often simply referred to as a “follicular neoplasm” by the cytopathologist. The diagnosis of cancer may be made only after the review of the permanent histologic sections shows tumor capsule invasion by follicular cells, thus posing a serious management predicament at the time of surgery (Mazzaferri, 1993a).

Highly invasive follicular carcinomas are much less common. They are often recognized at surgery by their aggressive growth into surrounding tissues and extensive blood vessel invasion. Up to 80% of these cancers metastasize, causing death in as many as 20% of patients, often within a few years of diagnosis (Mazzaferri, 1993b). The poor prognosis is closely related to the patient's older age at the time of diagnosis, advanced tumor stage, and larger tumor size (Mazzaferri and Jhiang, 1994).

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 (less than 1.0 centimeter), or are minimally invasive. Both papillary and follicular carcinomas have poor outcomes if they are highly invasive or develop distant metastases (Brennan et al, 1991; Mazzaferri and Jhiang, 1994).

When Hürthle (oncocytic) cells constitute most or all of a 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 (Hedinger, 1993). Similar to follicular carcinoma, the differentiation between benign and malignant Hürthle tumors is often impossible to diagnose by FNA or frozen section study, although large (greater than 4 centimeter) tumors are more likely to be malignant (Chen et al, 1998). Some consider Hürthle cell carcinomas to be aggressive and unpredictable tumors with a mortality rate as high as 25% in 30 years (Thompson et al, 1973). Others believe these cancers are no more aggressive than similarly staged follicular carcinomas without Hürthle cells (Khafif et al, 1999). In the NCDB report, the 10-year relative survival rates were 85% for follicular and 76% for Hürthle cell carcinoma (Hundahl et al, 1998).

In two large series, pulmonary metastases occurred in 25% and 35% of patients with Hürthle cell carcinoma, about twice the frequency of follicular carcinoma metastases (Ruegemer et al, 1988; Samaan et al, 1992). Fewer Hürthle cell carcinomas concentrate I 131 than papillary or follicular carcinomas do. In a series of 100 patients with distant metastases reported from the M. D. Anderson Cancer Center (Samaan et al, 1985), I 131 uptake by pulmonary metastases was seen in over half the follicular (64%) and papillary (60%) carcinomas, but in only 36% of Hürthle cell carcinomas.

Primary Tumor Size: Papillary carcinomas smaller than 1 centimeter, termed “microcarcinomas,” are typically found unexpectedly after surgery for benign thyroid conditions. Their recurrence and cancer-specific mortality rates are near zero (Moosa and Mazzaferri, 1997; Baudin et al, 1998).

Other small papillary carcinomas that are biologically more virulent become clinically manifest. For example, about 20% of microcarcinomas are multifocal tumors that commonly metastasize to cervical lymph nodes. Some report a 60% rate of nodal

metastases from multifocal microcarcinomas (Sugino et al, 1998), which may be the presenting feature and also may be associated with distant metastases (Baudin et al, 1998). Otherwise, small (less than 1.5 centimeter), but clinically apparent, papillary or follicular carcinomas almost never cause distant metastases. Recurrence rates after 30 years are one third those associated with larger tumors and 30-year cancer-specific mortality is 0.4% compared to 7% ($P < .001$) for tumors 1.5 centimeters or larger (Mazzaferri and Jhiang, 1994).

The prognosis is incrementally poorer as tumors increase in size and this is true for both papillary (Hay, 1990) and follicular carcinomas (Brennan et al, 1991). There is a linear relationship between tumor size, recurrence, and cancer-specific mortality for both papillary and follicular carcinomas ([Figure 2](#)) (Mazzaferri and Jhiang, 1994).

Local Tumor Invasion: Up to 10% of differentiated thyroid carcinomas grow directly into surrounding tissues, increasing both morbidity and mortality. The invasion may be microscopic or gross and can occur with both papillary and follicular carcinomas (Emerick et al, 1993; Mazzaferri and Jhiang, 1994). Recurrence rates are two times higher with invasive than noninvasive tumors. Up to one third of patients with invasive tumors die of cancer within a decade (Salvesen et al, 1992; Mazzaferri and Jhiang, 1994).

Lymph Node Metastases: In one review, nodal metastases were found in 36% of 8,029 adults with papillary carcinoma, in 17% of 1,540 patients with follicular carcinoma, and in up to 80% of children with papillary carcinoma (Mazzaferri, 1993b). An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In such a patient, multiple nodal metastases are usually found at surgery.

The prognostic importance of regional lymph node metastases is controversial. Some studies find the presence of regional lymph node metastases has no impact on recurrence or survival (Hay et al, 1993; Shaha et al, 1995; Cady, 1998). Other studies find nodal metastases are a risk factor for local tumor recurrence and cancer-specific mortality and 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 (Mazzaferri and Jhiang, 1994; Yamashita et al, 1997; Tsang et al, 1998).

In one study, 15% of patients with cervical node metastases and none without died of thyroid carcinoma ($P < .02$) (Sellers et al, 1992). Another study of patients with distant metastases from papillary carcinoma reported that 80% had mediastinal node metastases at the time cancer was diagnosed (Lindegaard et al, 1988). 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 did those patients without metastases (6%) (Mazzaferri and Jhiang, 1994).

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 half of these metastases are present at the time of diagnosis (Mazzaferri, 1993b). Distant metastases occur even more often among patients with Hürthle cell cancer (35%) and those patients diagnosed after 40 years of age (Samaan et al, 1985; Ruegemer et al, 1988). The sites of reported distant metastases among 1,231 patients in 13 studies were lung (49%), bone (25%), both lung and bone (15%), and the central nervous system or other soft tissues (10%) (Mazzaferri,

1993b). The main influences on the outcome in patients with distant metastases are patient's age, the tumor's metastatic site, ability to concentrate I 131, and morphology on chest x-ray (Samaan et al, 1985; Ruegemer et al, 1988; Schlumberger et al, 1995; Sisson et al, 1996).

Although some patients--especially younger patients--with distant metastases survive for decades, about half die within 5 years regardless of tumor histology (Mazzaferri, 1993b). Even so, some pulmonary metastases are compatible with long survival. For example, one study found that when distant metastases were confined to the lung, over half the patients were alive and free of disease at 10 years, whereas no patient with skeletal metastases survived that long (Brown et al, 1984).

The survival rates are highest in young patients with diffuse lung metastases seen only on I 131 imaging and not on x-ray (Brown et al, 1984; Sisson et al, 1996), which appears to be the most important feature governing an improved survival rate and prolonged disease-free interval with lung metastases (Casara et al, 1993). Prognosis is worse with large pulmonary metastases that do not concentrate I 131, and is intermediate with small nodular metastases seen on x-ray that do concentrate I 131 (Samaan et al, 1985; Ruegemer et al, 1988; Schlumberger et al, 1995).

Tumor Staging and Prognostic Scoring Strategies

Several staging and clinical prognostic scoring strategies use patient age over 40 years as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma (American Joint Committee on Cancer, 1992; Hay et al, 1993; Cady, 1997; Sherman et al, 1998). Four of the schemes using age (EORTC, TNM, AMES, and AGES), when applied to the papillary carcinoma data from the Mayo Clinic, 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% (Hay, 1990). With incrementally worsening MACIS (metastasis, age, completeness of resection, invasion, size) scores of less than 6, 6 to 6.99, 7 to 7.99, and 8+, the 20 year survival rates were progressively lower--99%, 89%, 56%, and 24%, respectively (Hay et al, 1993).

However, a study that classified 269 patients with papillary carcinoma according to five different prognostic scoring schemes found that some patients in the lowest risk group for each scheme died of cancer (DeGroot et al, 1994). This is particularly true of the schemes that simply categorize patients dichotomously as low or high risk (Cady et al, 1979; American Joint Committee on Cancer, 1992). The American Joint Commission on Cancer (AJCC) TNM staging approach ([Table 1](#)), which is perhaps the most widely used scheme, classifies tumors in all patients under age 45 years as stage I or stage II (i.e., low risk), even those with distant metastases. Although it has been widely verified to predict cancer mortality (Loh et al, 1997; Lin et al, 1998), TNM staging does not forecast the high number of recurrences that occur in patients diagnosed before 20 years of age, which is true of all prognostic scoring systems that lend heavy weight to age. Moreover, all prognostic schemes fail to identify variants of papillary and follicular carcinoma that significantly affect outcome. Thus, two studies demonstrated the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system (Brierley et al, 1997; Sherman et al, 1998).

Perhaps the greatest utility of staging systems is in epidemiology studies and as tools to stratify patients for prospective trials (Sherman, 1999a). Staging systems are least useful in determining

treatment for individual patients. Because of this, many prefer total thyroidectomy, often followed by I 131 ablative therapy in (1) patients with papillary and follicular thyroid carcinoma more advanced than the T1, N0, M0 category, regardless of the patient's age; (2) multicentric tumors; and (3) the majority of patients with follicular thyroid carcinoma (Mazzaferri and Jhiang, 1994; Loh et al, 1997).

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 guideline does not use TNM stages to guide therapy, partly because of the dependence of TNM staging upon age as a dichotomous variable. Instead, tumor stage plays the dominant role in these guidelines. There is evidence that many practicing physicians already follow this paradigm. Several international surveys, including one by the clinical members of the American Thyroid Association, indicate that the majority of clinicians do not factor age into their therapeutic decisions (Van De Velde et al, 1988; Baldet et al, 1989; Solomon et al, 1996). This is a view held by the majority of the NCCN guidelines panel participants.

Initial Management of Differentiated Thyroid Carcinoma

Ipsilateral Lobectomy Versus Total or Near-total Thyroidectomy

The continuing debate about the extent of initial thyroid resection mainly centers on the poor predictive value of prognostic scoring (Cady et al, 1998). For example, Hay and associates reported in 1997 that patients treated at the Mayo Clinic for low risk papillary thyroid carcinomas (MACIS score less than or equal to 3.99) had no improvement in survival rates after undergoing more than ipsilateral lobectomy and, accordingly, concluded that more extensive surgery was indicated only for those with higher MACIS scores (Hay et al, 1987).

In 1998, however, Hay and associates reported the results of a study designed to compare cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy in patients with papillary carcinoma considered to be low risk by AMES (age, metastases, extent, size) criteria (Hay et al, 1998). Although there were no significant differences in cancer-specific mortality or distant metastasis rates between the two groups, the 20 year rates for local recurrence and nodal metastasis after unilateral lobectomy were 14% and 19%, significantly higher ($P = .0001$) than the 2% and 6% rates 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 to patients with low risk papillary carcinoma. Some individuals do not concur with this view, justifying unilateral lobectomy for nearly all patients with papillary and follicular thyroid carcinoma on the basis of the low mortality rates in those categorized as low risk by the AMES or TNM classification schemes (i.e., the majority of patients) and the high complication rates with more extensive thyroidectomy (Shaha et al, 1995; Cady, 1997).

When the diagnosis of thyroid carcinoma is known preoperatively, most advise total or near-total thyroidectomy for all patients (Schlumberger, 1998) because it improves disease-free survival, even in children and adults with low-risk tumors (Mazzaferri, 1991; Hay et al, 1998; Miccoli et al, 1998; Newman et al, 1998). Some find that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe (Hay et al, 1987; Mazzaferri, 1993b), an overall long term recurrence rate over 30% (versus 1% after total thyroidectomy and I 131 therapy) (Mazzaferri and Jhiang, 1994), and the highest frequency (11%) of subsequent pulmonary metastases (Massin et al, 1984). Higher recurrence

rates are also observed with cervical lymph node metastases and multicentric tumors, providing justification for more complete initial thyroid resection (Mazzaferri and Jhiang, 1994).

Nevertheless, most feel that lobectomy alone is adequate surgery for papillary microcarcinomas provided the patient has not been exposed to radiation and has no other risk factors, and that the tumor is smaller than 1 centimeter, unifocal, and confined to the thyroid without vascular invasion (Mazzaferri and Jhiang, 1994; Moosa and Mazzaferri, 1997; Baudin et al, 1998). The same is true for minimally invasive follicular cancers smaller than 4 centimeters. The large thyroid remnant, however, hampers long term follow-up with serum thyroglobulin (Tg) determinations and whole-body I 131 scans. The decision to forgo complete thyroidectomy should be made in consultation with the patient.

Completion Thyroidectomy

Completion thyroidectomy should be considered for tumors that have the potential for recurrence because large thyroid remnants are difficult to ablate with I 131 (Massin et al, 1984). Completion thyroidectomy has a low complication rate and is appropriate to perform routinely for tumors 1 centimeter or larger because approximately one half of the patients with tumors this size have residual cancer in the contralateral thyroid lobe. (DeGroot and Kaplan, 1991; Mettlin et al, 1991; Pasiaka et al, 1992; Emerick et al, 1993; Scheumann et al, 1996; Chao et al, 1998).

When there has been a local or distant tumor recurrence after lobectomy, residual cancer is found in over 60% of the excised contralateral lobes (Pasiaka et al, 1992). A study of irradiated children from Chernobyl who developed thyroid carcinoma and were treated by lobectomy found that 61% had unrecognized lung or

lymph node metastases that could only be identified after completion thyroidectomy (Miccoli et al, 1998). In another study, patients who underwent completion thyroidectomy within 6 months of their primary operation developed significantly fewer lymph node and hematogenous recurrences and survived significantly longer than did those in whom the second operation was delayed for more than 6 months (Scheumann et al, 1996).

Surgical Complications

The main complications of thyroidectomy--hypoparathyroidism and recurrent laryngeal nerve damage--occur most commonly after total thyroidectomy. The rates of hypoparathyroidism immediately after surgery are as high as 5% in adults (Burge et al, 1998) and are even higher in children (Dralle et al, 1998; Miccoli et al, 1998) undergoing total thyroidectomy. The rates of persistent hypocalcemia, however, are much lower. In a review of seven published surgical series, the average rates of permanent recurrent laryngeal nerve injury and hypoparathyroidism, respectively, were 3% and 2.6% after total thyroidectomy and 1.9% and 0.2% after subtotal thyroidectomy (Udelsman et al, 1996). The rates of persistent hoarseness and hypoparathyroidism were lower.

One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later (Pattou et al, 1998). When experienced surgeons perform the surgery and the posterior thyroid capsule is left intact on the contralateral side, hypoparathyroidism occurs at a lower rate. A study of 5,860 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 the procedure fewer than 10 times a year had four times the rate of complications (Sosa et al, 1998).

Adjuvant Radioiodine Therapy

Postoperative I 131 remnant ablation is performed when the patient has a tumor with the potential for recurrence (Mazzaferri, 1997). Studies demonstrate decreased recurrence and disease-specific mortality when postoperative I 131 therapy is administered as part of the initial treatment (DeGroot et al, 1994; Mazzaferri and Jhiang, 1994; Mazzaferri, 1997; Taylor et al, 1998; Tsang et al, 1998). In a study comparing outcomes in 1,004 patients with differentiated thyroid carcinoma, tumor recurrence was about threefold higher in those patients who were treated with thyroid hormone alone or given no postoperative medical therapy compared to patients who underwent postoperative thyroid remnant ablation with I 131 ($P < .001$). Moreover, fewer patients developed distant metastases ($P < .002$) after thyroid I 131 ablation than after other forms of postoperative treatment--an effect observed only in patients with primary tumors smaller than 1.5 centimeters in diameter (Mazzaferri, 1997). Some find less of a therapeutic effect of remnant ablation, perhaps because more extensive thyroidectomy had been done (Hay, 1990).

Although there continues to be debate about ablating the thyroid bed with I 131 after near-total thyroidectomy (Hay, 1990; Mazzaferri, 1997), there are three compelling reasons to do this in addition to attempting to treat microscopic residual disease:

1. If total or near-total thyroidectomy has been performed in an attempt to remove all or nearly all thyroid tissue, it is often necessary to ablate the thyroid remnant with I 131. It is

nearly impossible to remove all thyroid tissue with routine surgery. This accounts for the uptake of I 131 that is almost always seen in the thyroid bed postoperatively and often must be ablated before I 131 will optimally concentrate in cervical or pulmonary metastatic deposits (Miccoli et al, 1998).

2. High circulating TSH levels, necessary to enhance tumor I 131 uptake, cannot be achieved with a large thyroid remnant (Goldman et al, 1980).

3. Serum Tg measurements are the most sensitive tests for cancer when there is no normal thyroid tissue present and Tg is measured during hypothyroidism after the thyroid bed uptake has been ablated (Spencer et al, 1998).

Diagnostic Whole-body Scans and Thyroid “Stunning”

Whole-body I 131 scans are often performed after surgery to assess the completeness of thyroidectomy and the presence of residual disease. Due to follicular cell damage induced by large scanning doses of I 131, however, a phenomenon termed “stunning” occurs. Stunning decreases uptake in the thyroid remnant or metastases for several weeks, thus impairing the therapeutic efficacy of I 131 (Leger et al, 1998).

Small (2 or 3 mCi) doses of I 131 or the use of ¹²³I have been recommended to avoid the stunning effect, but they are less sensitive than larger scanning I 131 doses in identifying thyroid remnants (Muratet et al, 1997; Leger et al, 1998). Although some recommend that diagnostic I 131 scans be avoided completely, others argue a whole-body I 131 diagnostic scan should be performed because the results determine the optimal I 131 dose to ablate residual thyroid tissue or cancer (Mazzaferrri, 1996).

Radioiodine Therapy

There are three approaches to I 131 therapy: empiric fixed doses, quantitative dosimetry, and upper bound limits that are set by blood dosimetry (Brierley and Maxon, 1998).

Fixed I 131 Doses: The most widely used and simplest method is to administer a fixed dose. Most clinics use this method regardless of the percentage uptake of I 131 in the remnant or metastatic lesion. Patients with uptake in tumor are routinely treated with large, fixed amounts of I 131.

Lymph nodes metastases that are not large enough to excise are treated with about 100 to 175 mCi (3,700 to 6,475 MBq). Cancer growing through the thyroid capsule is treated with 150 to 200 mCi (5,550 to 7,400 MBq). Patients with distant metastases are usually treated with 200 mCi (7,400 MBq) I 131, which will not induce radiation sickness or produce serious damage to other structures.

Diffuse pulmonary metastases that concentrate 50% or more of the diagnostic dose of I 131 (which is very uncommon) are treated with 75 mCi (2,775 MBq) I 131 to avoid lung injury.

Quantitative Tumor I 131 Dosimetry: A second approach is to use quantitative dosimetry methods to estimate tumor uptake. Some favor this approach because radiation exposure from arbitrarily fixed doses of I 131 can vary considerably. If the calculated dose to the tumor is less than 3,500 cGy, it is unlikely that the cancer will respond to I 131 therapy (Maxon et al, 1992; Brierley and Maxon, 1998).

Radioiodine activities that will deliver substantial doses to the residual normal tissue and 4,000 to 5,000 cGy to metastatic foci are likely to be effective. It is necessary to estimate tumor size to make

these calculations, which is difficult to do with diffuse lung metastases. Lesions that receive only a few hundred cGy from 150 to 200 mCi (5,550 to 7,400 MBq) I 131 should be considered for surgery, external radiation, or medical therapy.

Blood I 131 Dosimetry: A third method is to administer a dose calculated to deliver a maximum of 200 cGy to the blood, keeping the whole-body retention less than 120 mCi (4,440 MBq) at 48 hours and the amount in the lungs less than 80 mCi (2,960 MBq) when there is diffuse pulmonary uptake. The maximum administered dose is kept at 300 mCi (11,100 MBq) (Benua et al, 1962).

Hospitalization was required in the past to administer therapeutic doses of I 131 larger than 30 mCi (1,110 MBq). This is no longer necessary in most states because a change in federal regulations permits the use of much larger I 131 doses in ambulatory patients (Brierley and Maxon, 1998).

Posttreatment I 131 Scans

Metastases often do not concentrate much I 131, or may not concentrate it at all, when much normal thyroid tissue is present (Vassilopoulou-Sellin et al, 1993; Miccoli et al, 1998). When I 131 therapy is given, a whole body scan should be performed to document I 131 uptake by the tumor. The whole body scan should be done primarily because about 25% of posttreatment scans show lesions not detected by the diagnostic scan, which may or may not be clinically important (Brierley and Maxon, 1998).

In a study of pretreatment and posttreatment scans, the two differed in 27% of the treatment cycles, but only 10% of the posttreatment scans showed clinically significant new foci of metastatic disease (Sherman et al, 1994). Posttreatment scans were most likely to reveal clinically important new information in patients under age 45

years who had received I 131 therapy in the past. On the contrary, in older patients and those patients who had not previously received I 131 therapy, the posttreatment scans rarely yielded new information that might have altered the patient's prognosis (Sherman et al, 1994).

Assessment and Management After Initial Treatment

Serum Tg determinations and whole-body I 131 imaging together will detect recurrent or residual disease in most patients who have undergone total thyroid ablation. In contrast, both studies are insensitive in patients who have undergone lobectomy. When initial ablative therapy has been completed, serum Tg should be measured periodically and whole-body I 131 scanning done after thyroxine therapy is discontinued or recombinant human TSH (rhTSH) is administered. Serum Tg can be measured while the patient is taking thyroxine, but the test is more sensitive when thyroxine has been stopped or rhTSH is given to elevate the serum TSH (Pacini et al, 1985; Haugen et al, 1999).

Recombinant Human TSH

During follow-up, periodic withdrawal of thyroid hormone therapy is required to raise the serum TSH concentrations sufficiently to stimulate thyroid tissue so that serum Tg measurements and I 131 scanning can be performed to detect residual thyroid tissue or carcinoma. This can be done by withdrawing thyroid hormone, causing symptomatic hypothyroidism, or by administering rhTSH intramuscularly, stimulating thyroidal I 131 uptake and Tg release. Meanwhile, the patient continues thyroid hormone suppression therapy, thus avoiding symptomatic hypothyroidism (Ladenson et al, 1997). The drug has been approved for diagnostic use and has been tested in two large international multicenter studies.

The first study found that whole-body I 131 scan results after two 0.9-mg doses of rhTSH, given while thyroid hormone was continued, were of good quality and equivalent to the scans obtained after thyroid hormone withdrawal in 66% of the patients, superior in 5% of patients and inferior in 29% (Ladenson et al, 1997). Although this study proved that rhTSH stimulates I 131 uptake for whole body scanning, the sensitivity of I 131 scanning after rhTSH administration was less than after the withdrawal of thyroid hormone (Ladenson et al, 1997).

A second multicenter international study was performed to test the effects of two dosing schedules of rhTSH on whole body I 131 scans and serum Tg levels compared with those scans obtained after thyroid hormone withdrawal. The scanning method in this study was more carefully standardized and took into account the fact that I 131 retention was higher in patients rendered hypothyroid than in those patients given rhTSH (Haugen et al, 1999). Scans were concordant in 89% of the patients and superior in 4% of the patients after rhTSH and in 8% of patients after thyroid hormone withdrawal--differences that 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 patients with metastatic carcinoma (Haugen et al, 1999).

Recombinant human TSH, 0.9 mg, is given intramuscularly every day for 2 days, followed by a minimum of 4 mCi of I 131 on the third day. A whole body scan and Tg measurements are performed on the fifth day. Whole body I 131 images are acquired after 30 minutes of scanning or after obtaining 140,000 counts because a 4 mCi dose of I 131 may have the same body retention as a 2 mCi

dose given to a hypothyroid patient. A serum Tg of 2.5 ng/mL or higher obtained 72 hours after the last rhTSH injection indicates that thyroid tissue or thyroid carcinoma is present, which almost always can be identified on the rhTSH-stimulated whole body scan, provided one follows the scanning procedure noted above (Haugen et al, 1999). The drug is well tolerated. Nausea (10.5%) and transient mild headache (7.3%) are its main adverse effects (Haugen et al, 1999). It is associated with significantly fewer symptoms and dysphoric mood states compared with hypothyroidism induced by thyroid hormone withdrawal (Ladenson et al, 1997).

Measuring Serum Thyroglobulin

Serum Tg measurement is the best means of detecting thyroid tissue--both normal and malignant. Although there are no other sources of Tg to falsely elevate it, antithyroglobulin 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 (Spencer et al, 1998).

Thyroglobulin should be measured when TSH has been stimulated by thyroid hormone withdrawal or rhTSH stimulation, when serum Tg has a lower false-negative rate than whole body I 131 scanning (Pacini et al, 1985; Haugen et al, 1999). Detecting the presence of circulating thyroid cells by a newly introduced Tg mRNA method may be a more sensitive marker of residual thyroid tissue or cancer than measuring Tg by immunometric assay, especially when Tg mRNA is detected during thyroxine treatment or with circulating antithyroglobulin antibodies, but this procedure is not yet commercially available (Ringel et al, 1998).

In a study of serum Tg measurements in 180 patients who had undergone near-total or total thyroidectomy and I 131 ablation and were followed up to 18 years, 94% had Tg values less than 5 ng/mL and 98% had values less than 10 ng/mL during thyroxine therapy (Ozata et al, 1994).

Studies show the results of serum Tg and I 131 tests are complementary. Patients rarely have recurrent carcinoma after they have undergone near-total or total thyroidectomy and I 131 ablation and have two negative post-ablation scans and undetectable serum Tg values while receiving thyroxine and, after thyroxine is discontinued, Tg values of less than 5 ng/mL (Ringel et al, 1998). The sensitivity and specificity of various Tg assays, however, vary widely in different laboratories, even with the use of a new international standard (CRM 457) (Spencer et al, 1996).

Treating Thyroglobulin-Positive/Scan-Negative Patients

Posttreatment I 131 scans are most likely to yield critical information when the serum Tg level is elevated and a tumor cannot be found by physical examination or localizing techniques, such as diagnostic I 131 scans, neck ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans. Pulmonary metastases may be found only after administering therapeutic doses of I 131 and obtaining a whole body scan within a few days of treatment (Schlumberger et al, 1997). In a study of 283 patients treated with 100 mCi (3,700 MBq) I 131, 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) scans (Schlumberger et al, 1986).

In another study, all but 1 of 17 patients with elevated serum Tg concentrations and negative 5-mCi (185 MBq) diagnostic scans

showed I 131 uptake after 75 to 140 mCi (2,775 to 5,180 MBq) I 131; more than one half of these patients had lung metastases (Pacini et al, 1987). Treatment of these lesions usually reduces the tumor burden, but their complete eradication may be difficult to achieve (Pineda et al, 1995). The Tg level that is used for recommending treatment has been coming down; it was about 30 or 40 ng/mL about a decade ago, but now is approximately 10 ng/mL (Mazzaferri, 1995; Schlumberger et al, 1997). However, no study has yet demonstrated any reduction in morbidity or mortality in patients treated with I 131 on the basis of elevated Tg measurements alone and potential side effects may negate any benefit.

Thyroid Hormone Suppression of TSH

Recurrence rates and cancer-specific mortality rates of differentiated thyroid carcinoma are significantly reduced in patients treated with thyroid hormone (Mazzaferri and Jhiang, 1994; Mazzaferri, 1997). The dosage needed to attain serum TSH levels in the euthyroid range is higher in patients with thyroid carcinoma (2.11 µg/kg/day) than in those patients with spontaneously occurring primary hypothyroidism (1.62 µg/kg/day) (Burmeister et al, 1992). Still, the optimal TSH level to be achieved in patients with thyroid carcinoma is uncertain.

A French study found that a constantly suppressed TSH level (0.05 mU/mL or less) was associated with a longer relapse-free survival than when serum TSH levels were always 1 mU/mL or higher. Furthermore, the degree of TSH suppression was an independent predictor of recurrence (Pujol et al, 1996). Similarly, a prospective U.S. study of 617 patients by the National Thyroid Cancer Treatment Cooperative Study Group found that TSH suppression improved progression-free survival in high risk, stage III and stage IV patients (Cooper et al, 1999).

These data do not support the concept that excessive TSH suppression (into the undetectable, thyrotoxic range) is required to prevent disease progression, however. As a practical matter, the most appropriate dose of thyroid hormone for most patients with differentiated thyroid carcinoma is that dose which reduces the serum concentration to just below the lower limit of the normal range for the assay being used.

Adjuvant External Radiation Therapy

Two studies show that adjuvant external radiotherapy (in addition to total thyroidectomy, with or without treatment with radioiodine, and TSH-suppressive therapy with thyroid hormone) improves the recurrence-free survival in patients older than 40 years of age with invasive papillary thyroid cancer (T4) and lymph node involvement (N1) (Farahati et al, 1996; Tsang et al, 1998). Patients with microscopic residual papillary carcinoma after surgery are more commonly rendered disease-free after receiving external radiotherapy (90%) than when not receiving it (26%) (Simpson et al, 1988).

This is also true of patients with microscopically invasive follicular carcinoma who are more often disease-free when postoperative external radiation is given (53%) than when it is not given (38%) (Simpson et al, 1988). Following surgery that left no macroscopic residue papillary cancer, 20% of patients treated with 4,500 cGy had a recurrence and none died. Lower doses were not beneficial (Ésik et al, 1994). Patients with follicular carcinomas treated with higher doses had only a 2% recurrence rate. External radiation did not alter mortality.

Adjuvant Chemotherapy and Surgical Excision of Metastases

Focal lesions that do not concentrate I 131 adequately and isolated

skeletal metastases should be considered for surgical excision or external irradiation. Brain metastases pose a special problem because I 131 therapy may induce cerebral edema. Once brain metastases are diagnosed, disease-specific mortality is very high (67%), with a median survival of 12.4 months in one retrospective study, which was significantly improved by surgical resection of one or more tumor foci (Chiu et al, 1997).

Life-threatening tumors refractory to all other forms of therapy may be palliatively treated with doxorubicin, although the response rate is poor (Mazzaferri, 1993b). The experience with chemotherapy in patients with differentiated thyroid carcinoma is limited because most recurrent tumors respond well to surgery, I 131 therapy or external beam radiotherapy. Chemotherapy's main use is for tumors that are not surgically resectable, are not responsive to I 131, and have either been treated with or are not amenable to therapy with external beam radiotherapy.

Among 49 patients with metastatic differentiated thyroid carcinoma treated with five chemotherapy protocols, only two (3%) patients had objective responses (Droz et al, 1990). In a review of published series, 38% of patients had a response defined as a reduction in tumor mass) to doxorubicin (Ahuja and Ernst, 1987). Combination chemotherapy is not clearly superior to doxorubicin therapy alone (Mazzaferri, 1993b).

Clinical Presentation and Initial Evaluation

Features of the clinical presentation of thyroid carcinoma are listed in the algorithms included with this guideline. The panel designated a thyroid nodule over 1 centimeter in diameter as clinically suspicious. Other characteristics may increase suspicion. These characteristics include: (1) the nodule's characteristics on physical

examination, (2) male gender, (3) age less than 15 years or greater than 45 years, (4) family history of thyroid carcinoma, (5) a history of diseases related to thyroid carcinoma (e.g., pheochromocytoma, hyperparathyroidism, Gardner's syndrome, Carney complex, Cowden's syndrome, and Familial adenomatous polyposis), and (6) the presence of confounding factors such as a history of head or neck irradiation. Nodules less than 1 cm in diameter are considered clinically nonsuspicious.

Before any imaging studies are done in a clinically euthyroid patient, FNA of the nodule or clinically suspicious lymph nodes is recommended as the first diagnostic test. Although the guidelines recommend that FNA yielding cytology that is insufficient for diagnosis should be repeated, it is silent about nodules that persistently yield insufficient specimens for diagnosis. This situation requires careful clinical judgment. In most cases a surgical biopsy will be needed. The result of the insufficient FNA would be to consider using ultrasound guidance for a repeat FNA. Repeat FNA is not recommended for nodules that yield an abundance of follicular cells with little or no colloid, categorized as follicular neoplasm or Hürthle cell neoplasm, and which require surgery because approximately 20% are minimally invasive follicular carcinomas (discussed above under the heading “Initial Work-up”). The guidelines provide a paradigm to identify patients with low TSH and a “hot” nodule on thyroid scan who can be spared surgery. It should be noted the recommendation for benign lesions does not suggest repeat FNA unless the nodule shows evidence of growth. Although there is some controversy about the use of thyroid hormone therapy for benign thyroid nodules, shrinkage of a nodule with thyroxine therapy should not be used as a diagnostic test.

Papillary Thyroid Carcinoma

Surgical Therapy

Workup prior to surgery should include a chest x-ray and a CT/MRI if the lesion is fixed or substernal (iodinated contrast should be avoided unless essential). A neck ultrasound may provide additional information.

The panel members agreed on the definition of high-risk patients who require total thyroidectomy and lymph node dissection (if nodes are positive) as the primary treatment. There is a category 3 recommendation about the preferred primary surgery for patients who are considered to be at moderate or low risk of cancer-specific mortality. The majority of panel members opted for total thyroidectomy in any patient in whom papillary thyroid carcinoma was identified preoperatively or at the time of surgery, whereas a minority of panel members felt strongly that, initially, lobectomy plus isthmectomy is adequate surgery for moderate and low risk patients (category 3). The pros and cons for this disagreement are discussed in detail under the heading “Initial Management of Differentiated Thyroid Carcinoma.”

The majority of clinicians appear to opt for total thyroidectomy for most patients, but this is perhaps the most widely debated issue in the treatment of thyroid carcinoma. This issue is discussed in detail in the “Initial Management of Differentiated Thyroid Carcinoma” section of this article. Aggressive variant disease (e.g., tall cell variant of papillary carcinoma) or multifocal disease warrant completion thyroidectomy.

For patients who undergo lobectomy plus isthmectomy (moderate to low risk patients), there was general agreement that positive

margins, clinically suspicious contralateral lesions, aggressive variant, or multifocal disease warrant consideration of a total thyroidectomy or completion thyroidectomy (category 3). The guidelines indicate that lobectomy is sufficient for small (less than 1 centimeter) papillary carcinomas found incidentally on the final pathology sections in the course of thyroid surgery for benign disease. However, incidentally discovered papillary carcinomas greater than 1 centimeter in size may warrant a completion thyroidectomy if there are positive margins, a clinically suspicious contralateral lesion, an aggressive variant, or multifocal disease.

Postoperative Whole-body I 131 Diagnostic Scans

The decision to perform a diagnostic whole-body I 131 scan before I 131 therapy is administered is a category 2B recommendation. The panel felt that this decision should be weighed against the problem of “stunning” that occurs with diagnostic I 131 scans (discussed above under the heading “Diagnostic Whole-body Scans and Thyroid ‘Stunning’”). The alternative to performing a diagnostic I 131 scan is to obtain a whole body scan a few days after treatment with I 131, termed as “posttreatment I-131 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. Although there is debate about the use of I 131 to ablate uptake in the thyroid bed after total thyroidectomy, the guidelines recommend doing so if the patient has undergone total thyroidectomy and there is I 131 uptake in the thyroid bed or the serum Tg is above 10 ng/dL (for practical purposes, this is almost

always accompanied by I 131 uptake on the scan). There are compelling reasons to ablate uptake in the thyroid bed after total thyroidectomy and those reasons are summarized in the section entitled “Thyroid Remnant Ablation.”

Radioactive Iodine Treatment

The three approaches to I 131 therapy--empiric fixed doses, upper bound limits set by blood dosimetry and quantitative dosimetry--are discussed in the “Radioiodine Therapy” section. Therapy with I 131 is advised for patients with tumors found on examination, imaging studies, or by elevated serum Tg levels that are not amenable to surgical removal and that concentrate I 131.

The postsurgical therapy recommendations include three options, based on serum Tg level and the results of a whole body I 131 scan, as well as the general level of agreement among the panel members for I 131 treatment recommendations. The panel agreed that for patients with both an elevated Tg level greater than 10 ng/mL and a positive whole body scan, I 131 treatment and a posttreatment I 131 scan should be completed. For patients with an elevated Tg level greater than 10 ng/mL or a positive whole-body scan, but not both, most panel members recommended that I 131 treatment and a posttreatment I 131 scan be considered. The third group of patients included those with negative tests for both Tg (i.e., a Tg value below 10 ng/mL) and the whole body scan. A minority of the panel members felt that therapy could be considered for these patients, but there was no consensus on this recommendation (category 3). The doses of I 131 are not specified in the guidelines except when recurrent disease is suspected on the basis of a high serum Tg value and negative imaging studies in which case an empiric fixed dose of 100 to 150 mCi of I 131 is recommended for consideration.

The guidelines recommend that posttreatment whole body scans be considered to assess the concentration of the isotope in tumor foci and to identify new areas of tumor growth not seen on diagnostic scans after I 131 therapy is administered for therapy.

Adjuvant External Radiotherapy

The guidelines recommend that external radiotherapy be considered for patients over 45 years of age with T4, N1 tumors and for tumor deposits that are not amenable to surgery (“surgically unresectable gross residual disease”) or do not concentrate I 131. The rationale for this recommendation may be found in the section entitled “Adjuvant External Radiation Therapy.”

Thyroxine Suppression of TSH

Thyroxine therapy is advised in the guidelines. The level of TSH suppression is not stipulated because there are conflicting data on this point. (See section entitled “Thyroid Hormone Suppression of TSH.”) As a practical matter, the most appropriate dose of thyroid hormone for most patients with differentiated thyroid cancer is that dose which reduces the serum TSH concentration to just below the lower limit of the normal range.

Surveillance and Maintenance

The guidelines recommend long term surveillance and maintenance with a physical exam every 3 to 6 months for 2 years, then annually if disease-free; regular diagnostic whole body I 131 scans every 12 months until 1 or 2 negative scans (either withdrawal of thyroid hormone or rh TSH) if total thyroidectomy and ablation; serum Tg measurements at 6 and 12 months, then annually if disease-free; consider periodic chest x-rays, and additional nonradioiodine

imaging if I 131 scans are negative and serum thyroglobulin is elevated more than 10 ng/mL on or off thyroxine therapy or more than 5 ng/mL after rh TSH. The panel acknowledges that the suggested Tg cutoff levels will continue to evolve as new Tg assays are introduced, in particular, measurement of Tg levels by amplification of Tg messenger ribonucleic acid (mRNA) in peripheral blood.

Serum antibodies directed at Tg do not interfere with the mRNA Tg test, which is important since these antibodies can seriously interfere with immunometric assays of serum Tg. The serum Tg levels recommended in the guidelines show different cutoff points in response to the rise in serum TSH following thyroid hormone withdrawal rhTSH stimulation. The Tg cutoff points are lower after rhTSH stimulation than with thyroid hormone withdrawal. The conditions for rhTSH-stimulated whole body I 131 scans stipulate using 4-mCi I 131 doses and a scanning time of 30 minutes or until 140,000 counts are obtained.

Recurrent Disease

The panel agreed that the first choice of therapy for recurrent disease is surgery if the tumor can be localized and is resectable. For locoregional recurrences that are not amenable to surgery, I 131 therapy is recommended for tumors that concentrate I 131 and/or external beam radiotherapy for those that do not.

For metastatic disease, several therapeutic approaches are recommended, depending upon the site and number of tumor foci. For skeletal metastases, surgery should be considered for symptomatic tumors or those in weight-bearing extremities. Other therapeutic options are

I 131 treatment (if the whole body scan is positive) and external beam radiotherapy, alone and in combination. Consideration may also be given to the use of biphosphate (pamidronate) for symptomatic metastases (category 2B). For solitary metastases to the central nervous system, surgical resection should be considered for appropriate cases, with or without radioiodine treatment (with rh TSH and steroid prophylaxis) if radioiodine scan is positive, and/ or external beam radiotherapy. For disseminated tumors, I 131 dosimetry should be considered if the tumor concentrates the radioisotope, or systemic chemotherapy if it does not. Since chemotherapy has been generally disappointing, the guidelines recommend consideration of clinical trials for tumors that do not concentrate I 131.

Follicular Thyroid Carcinoma

The main differences between pathology and prognosis of follicular and papillary thyroid carcinoma are summarized in the beginning of this article. Because there are many similarities in the diagnosis and treatment of papillary and follicular carcinoma, only the important differences in the management of follicular carcinoma are highlighted.

Treatment

Fine needle aspiration is not as specific for follicular thyroid carcinoma as it is for papillary carcinoma and accounts for the main differences in management of the two tumor types. Most often, the FNA cytologic diagnosis is “follicular neoplasm,” which is usually (80%) from a benign follicular adenoma. This diagnosis accounts for the recommendation for total thyroidectomy only if invasive cancer or metastatic disease is apparent at the time of surgery or if

the patient opts for total thyroidectomy in order to avoid a second procedure if cancer is found at pathologic review. Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery when the FNA cytology is interpreted as a follicular neoplasm. If invasive follicular carcinoma is found on the final histologic sections, prompt completion of thyroidectomy is recommended.

Completion thyroidectomy should be considered for tumors that, on final histologic sections, are minimally invasive follicular carcinomas larger than 4 centimeters. These tumors may also be simply followed carefully since minimally invasive follicular carcinomas rarely recur. 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 postoperatively for advanced lesions (T₁).

The decision to perform a diagnostic whole body I 131 scan before I 131 therapy is administered is a category 2B recommendation in the guidelines. This form of treatment is not recommended for follicular carcinoma related to the lack of evidence of benefit from adjuvant external beam radiotherapy.

Hürthle Cell Carcinoma

This tumor is a variant of follicular thyroid carcinoma, although the prognosis of Hürthle cell carcinoma is worse, as discussed under “Prognosis and Recurrence.” Hürthle cells also occur in a few papillary carcinomas. The management of this disease is almost identical to follicular carcinoma, except that Hürthle cell tumors are less likely to concentrate I 131. Postoperative RT may be used for advanced lesions.

The decision to perform a diagnostic whole body I 131 scan before I 131 therapy is administered is a category 2B recommendation.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) derives from the neuroendocrine parafollicular or C cells of the thyroid (Ball et al, 1996). 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 medullary thyroid carcinoma (FMTC). 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 (Saad et al, 1984).

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, symptoms of Cushing's syndrome, or facial flushing in many patients with advanced disease. Rarely, MTC is suggested by the presence of dense calcifications seen on radiologic imaging of the anterior neck or sites of metastatic disease. Sporadic disease typically presents in the fifth or sixth decade. There may be a slight female preponderance. Familial forms of the disease tend to present at earlier ages.

Diagnosis

The diagnosis of sporadic MTC is usually suspected following 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, recent reports suggest that perhaps as many as 3% of patients with nodular thyroid disease will have an elevated serum calcitonin level when measured by a sensitive immunometric assay. Forty percent (40%) of these patients will prove to have MTC at thyroidectomy (Pacini et al, 1994; Niccoli et al, 1997; Ozgen et al, 1999). At an estimated cost of \$12,500 per diagnosed MTC case that would not be identified by other means, routine measurement of the serum calcitonin concentration is not recommended for the evaluation of a patient with a thyroid nodule (Horvit and Gagel, 1997). For patients in known kindreds with inherited MTC, prospective family screening can identify disease carriers long before clinical symptoms or signs are noted (Gagel and Cote, 1998). Using the traditional approach of stimulated secretion of calcitonin by either pentagastrin or calcium infusion, 65% of MEN 2A gene carriers will have abnormal calcitonin levels by age 20 years. Ninety five percent (95%) will have an elevated calcitonin level by age 35 years (Ponder et al, 1988). 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 uncommonly 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 95% of kindreds with familial forms of MTC (Gagel and Cote, 1998). The RET proto-

oncogene codes for a cell membrane-associated tyrosine kinase receptor for glial-cell-line-derived neurotrophic factor. Mutations associated with MEN 2A and FMTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exon 10, 11, and 13, while MEN 2B and some FMTC mutations are found within the intracellular exons 15 and 16 ([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 (Wohllk et al, 1996).

Genetic testing for RET proto-oncogene mutations should be offered to all newly diagnosed patients with clinically apparent sporadic MTC, as well as for screening children and adults in known kindreds with inherited forms of MTC. Based on the relative frequency of mutations in certain exons, mutational analysis should start with exon 11, followed sequentially by exons 10, 16, 13, 14, and 15 (Gagel and Cote, 1998). Although common mutations can be identified by broadly available commercial testing sources, only a limited number of sites perform the more thorough analyses that are required to identify the less common mutations. A 3% to 5% error rate is generally reported, underscoring the importance for repeat testing of at least two independently-obtained blood samples in more than one laboratory to minimize the likelihood of both false-positive and false-negative results (Gagel et al, 1995).

Staging

Compared with differentiated thyroid carcinoma, a smaller set of staging approaches exist for MTC. The TNM criteria for

clinicopathologic tumor staging are based upon tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (Behrs et al, 1988). An MTC less than 1 centimeter in diameter without evidence of disease outside of the thyroid gland is considered stage I. Any larger tumor or the presence of extrathyroidal invasion without nodal or distant metastases is classified as stage II. Locoregional nodal metastases, regardless of tumor size, place the patient in stage III, and any distant metastases in stage IV. In one recent study with a median follow-up period of only 4 years, mortality due to MTC was 0% for stage I, 13% for stage II, 56% for stage III, and 100% for stage IV disease (Dottorini et al, 1996).

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 (DeGroot, 1975). Extrathyroidal or extranodal extension characterizes stage III disease and distant metastases, 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 due to MTC at least sevenfold and carries a median disease-specific survival of 3 to 5 years (Saad et al, 1984).

A third approach, used by the National Thyroid Cancer Treatment Co-operative Study Group (Sherman et al, 1998), defines stage I disease as the premalignant lesion C-cell hyperplasia, generally only identified as an incidental finding except as result of familial screening. Stage II disease is a primary tumor less than 1 centimeter without locoregional or distant metastasis. Stage III is a tumor greater than 1 centimeter or locoregional nodal metastasis. The presence of distant metastases defines stage IV disease.

Other important prognostic factors are lacking from these staging

classifications. Notably absent is consideration of age at diagnosis. Patients less than 40 years of age 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 of age (Saad et al, 1984). 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 (Samaan et al, 1988; O'Riordain et al, 1994). Despite an even younger typical age at diagnosis, patients with MTC in MEN 2B are more likely than those with either MEN 2A or FMTC to have locally aggressive disease (O'Riordain et al, 1994).

Other factors that may be important for predicting a worse prognosis include: (1) the heterogeneity and paucity of calcitonin immunostaining of the tumor (Lippman et al, 1982), (2) a rapidly rising serum carcinoembryonic antigen (CEA) level, particularly in the setting of a stable calcitonin level (Mendelsohn et al, 1984), and (3) postoperative residual hypercalcitoninemia (Dottorini et al, 1996). 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 (Maldonado and Sherman, 1999). 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 (Romei et al, 1996).

Initial Surgical Management

Even with patients who have apparently sporadic disease, the possibility of MEN 2 should be considered preoperatively and serum calcium and 24-hour urinary excretion of metanephrines and

catecholamines should be measured. Total thyroidectomy is indicated in all patients with MTC, especially in consideration of the high frequency of bilateral disease in both sporadic and familial disease (Saad et al, 1984). Once an MTC tumor is large enough to be palpated, there is a high frequency of metastasis to adjacent nodal tissue. Even in the absence of clinically detectable nodal metastases, central neck compartment dissection (Level VI) should be performed in all patients. Ipsilateral modified lateral neck (Levels II-V) and/or mediastinal dissections should be performed when the primary tumor is greater than 1 centimeter or central compartment disease is present. 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, but TSH suppression is not appropriate as C cells lack TSH receptors.

Adjuvant Radiation Therapy

External beam radiotherapy has not been adequately studied as adjuvant therapy in medullary carcinoma. Slight improvements have been reported in local disease-free survival following external beam radiotherapy for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement. However, most centers do not routinely administer such adjuvant therapy. When external beam radiotherapy is used, 40 Gy is typically administered in 20 fractions to the cervical, supraclavicular and upper mediastinal lymph nodes over 4 weeks, with subsequent booster doses of 10 Gy in five fractions to the thyroid bed (Brierley and Maxon, 1998). As for differentiated carcinoma, external beam radiotherapy can also be given to palliate painful bone metastases.

Persistently Elevated Calcitonin

Two or three months postoperatively, serum concentrations of calcitonin and CEA should be measured. Those patients whose calcitonin level is less than 10 pg/mL should undergo stimulation testing with a calcium infusion (Wells et al, 1985). About 80% of patients with palpable MTC and 50% of those with nonpalpable but macroscopic MTC who undergo supposedly curative resection have stimulated serum calcitonin values of at least 10 pg/mL, indicative of residual disease. Those patients with near-normal values can be followed. Those patients with values greater than 100 pg/mL should be evaluated for 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 no obvious MTC in the neck and upper mediastinum probably have distant metastases, most likely in the liver. 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 (van Heerden et al, 1990). Two more recent studies have reported higher mortality rates for patients with high postoperative serum calcitonin values, with more than half of patients having a recurrence during a mean follow-up of 10 years (Dottorini et al, 1996; Scopsi et al, 1996).

Given the general failure of routine lymphadenectomy or excision of palpable tumor to normalize the serum calcitonin concentrations in such patients, attention has been directed toward detection and eradication of microscopic tumor deposits. 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 (Tisell et al, 1986). 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 (Moley et al, 1998; Fleming et al, 1999).

Preoperative assessment should include ultrasonography of the neck; CT of the chest; MRI of the abdomen; bone scintigraphic imaging; and localization of disease by catheterization of the hepatic veins, both internal jugular veins and the innominate veins, with measurements of serum calcitonin before and after stimulation. Laparoscopic assessment of the liver may be performed if distant metastases are not detected by this diagnostic approach (Fleming et al, 1999). However, in the absence of long-term outcomes, application of this approach should probably be limited to those centers experienced in this procedure. Only patients with overt disease in the neck and no distant metastases should undergo re-operative neck surgery.

Prophylactic Surgery for Gene Carriers

Prophylactic thyroidectomy has been recommended for at-risk family members who are identified as carriers of a familial RET mutation (Wells Jr. and Skinner, 1998). Of 18 patients who underwent prophylactic thyroidectomy at a median age of 14 years, nearly 80% had a histologic diagnosis of MTC, but none had evidence of nodal metastases. In the 13 patients evaluated 3 years after surgery, all stimulated plasma calcitonin levels were normal. Given the identification of patients with malignant disease as early as age 6, most experts advocate prophylactic thyroidectomy before the age of 6 years in MEN 2A carriers (Chi and Moley, 1998; Evans et al, 1999). Virulence 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 mutation, annual provocative (calcium or pentagastrin) calcitonin testing might be continued, with total thyroidectomy and central node dissection deferred beyond 5 years of age until these tests become abnormal. Surveillance with stimulated calcitonin measurements, rather than surgery, is still suggested by some investigators for young gene carriers without evidence of MTC, although this approach should probably be avoided in children with the more virulent RET mutations in exons 10 and 11 (Gagel and Cote, 1998).

Clinical Presentation and Initial Evaluation

The panel recognized that patients with medullary carcinoma can be identified with clinical disease (i.e., pathologic diagnosis) or from prospective genetic screening. Separate paths are incorporated in the guideline depending upon the method of identification.

Generally accepted approaches to preoperative assessment include measurement of serum markers (calcitonin and CEA) and screening for pheochromocytoma and hyperparathyroidism. The panel underscored the importance of diagnosing and prospectively treating co-existing pheochromocytoma before undertaking surgical therapy for MTC. Preoperative ultrasound may be used in adults with clinical disease to evaluate for locoregional adenopathy, but there was disagreement regarding its use in young patients identified by prospective genetic screening, in whom the frequency of nodal metastases is quite low.

Surgical Therapy

Total thyroidectomy is the treatment of choice for all patients with MTC. If a patient with inherited disease is diagnosed early enough, the recommendation is total thyroidectomy be performed by age 5 years. Variations in surgical strategy depend on the risk for

locoregional node metastases and incorporation of simultaneous parathyroid resection for hyperparathyroidism. A bilateral central neck dissection (level VI) is preferred for all patients with pathologically demonstrated MTC and those with MEN 2B and should be strongly considered for patients identified by genetic testing. Bilateral central neck dissection (Level VI) for those patients with MEN 2A should be considered if there is an elevated calcium stimulated calcitonin test or ultrasound identified thyroid or nodal abnormality. Similarly, modified radical neck dissections (levels II to V) are recommended for all patients with primary tumors larger than 1 centimeter in diameter (0.5 centimeter for MEN 2B) or with tumor in the central node(s). With a concurrent diagnosis of hyperparathyroidism in MEN 2A, the surgeon should leave or autotransplant the equivalent mass of one 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.

Postoperative Management and Surveillance

Measurement of serum calcitonin and CEA levels is the cornerstone of postoperative assessment for residual disease. If a basal or unstimulated calcitonin level is undetectable in a sensitive immunoassay, then stimulation with calcium is necessary. Patients with undetectable calcitonin levels following stimulation can subsequently be followed with annual measurements of serum markers and consideration of periodic imaging only. If the patient is MEN 2B or 2A, annual screening for pheochromocytoma or hyperparathyroidism should also be performed. In contrast, if unstimulated serum markers are abnormal, there is no role for stimulation testing. Patients with abnormal serum markers should be considered for additional diagnostic imaging to identify the

location of tumor. The panel recognized that a wide variety of imaging modalities may be considered to examine for residual or metastatic tumor, but that there was 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 recommended conservative annual surveillance with repeat measurement of the serum markers. Repeat imaging studies may be considered periodically, including high resolution neck ultrasound scanning to examine both the thyroid bed and bilateral nodal chains. For asymptomatic patients with abnormal markers and repeated negative imaging, continued observation or consideration of cervical re-operation if incomplete primary surgery was performed is recommended. For the patient with rising serum markers, more frequent imaging may be considered. No therapeutic intervention is recommended on the basis of abnormal markers alone.

Recurrent or Persistent Disease

When locoregional disease is identified during surveillance testing, surgical resection is recommended. In the presence of distant metastases, locoregional disease should still be considered for removal. Similarly, distant metastases, such as those in bone, that are causing symptoms could be considered for resection. The panel also agreed that surgical excision may have a role for asymptomatic distant metastases, but that conservative observation is acceptable, given the lack of data regarding alteration in outcome.

In the setting of multiple or disseminated distant symptomatic metastases, the guidelines recommend consideration of several choices. External beam radiotherapy can be administered in the setting of focal symptoms. Systemic chemotherapy can be

considered, using dacarbazine or combinations including dacarbazine. When available, a clinical trial of investigational therapy should also be considered as an option for these patients.

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 about 65 years. Fewer than 10% of patients are younger than 50 years and 60% to 70% of patients are women (Gilliland et al, 1997). 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 (Moretti et al, 1997). No precipitating events have been identified and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain.

Patients with anaplastic carcinoma present with extensive local invasion and distant metastases are found at initial disease presentation in 15% to 50% of patients (Sherman, 1999b). 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.

The diagnosis of anaplastic carcinoma is usually established by FNA or surgical biopsy. Diagnostic procedures include a complete blood count, serum calcium, and TSH level. Computed tomography of the

neck and mediastinum can accurately determine the extent of the thyroid tumor and identify tumor invasion of great vessels and upper aero-digestive tract structures (Takashima et al, 1990). Most pulmonary metastases are nodules that can be detected by routine chest radiographs. Bone lesions are usually lytic.

Treatment and Prognosis

There is no effective therapy for anaplastic carcinoma and the disease is uniformly fatal. The median survival from diagnosis ranges from 3 to 7 months. The 1 and 5 year survival rates are about 25% and 5%, respectively (Sherman, 1999b). Death is attributable to upper airway obstruction and suffocation (often despite tracheostomy) in one half of these patients and to a combination of complications of local and distant disease and/or therapy in the remainder. 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 (Venkatesh et al, 1990). Other variables that may predict a worse prognosis include older age at diagnosis, male gender and dyspnea as a presenting symptom.

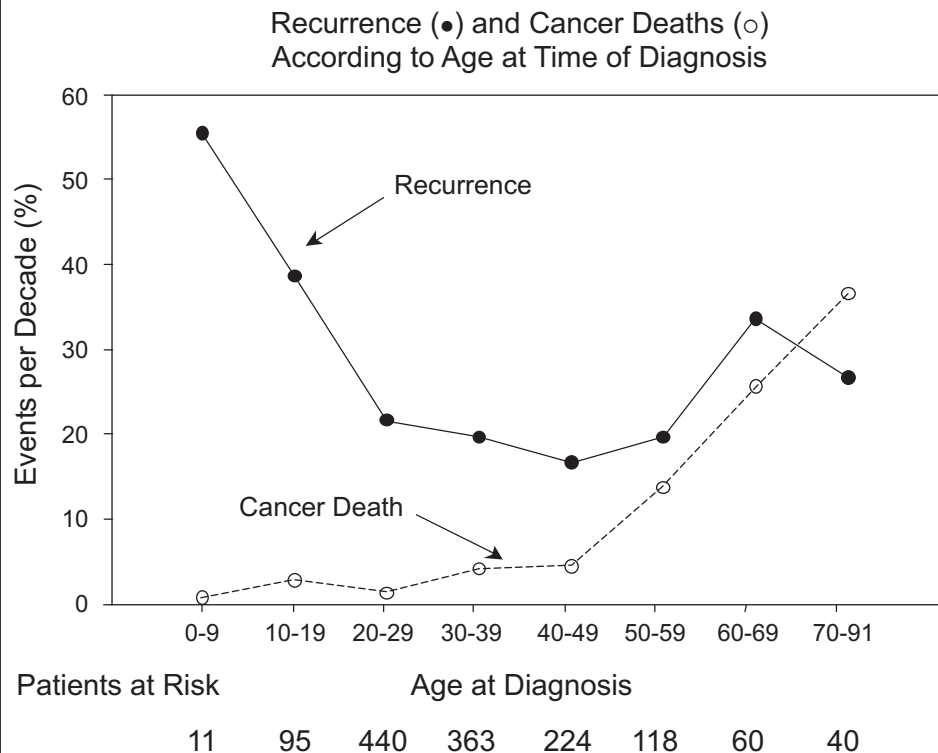
Except for patients whose tumors are small and confined entirely to the thyroid or readily excised structures, total thyroidectomy with complete tumor resection has not been shown to prolong survival (Venkatesh et al, 1990; Junor et al, 1992). External beam radiotherapy, administered in conventional doses, also does not prolong survival. Although up to 40% of patients may respond initially to radiation therapy, most have local recurrence. Treatment with single-drug chemotherapy also does not improve survival or control of disease in the neck, although perhaps 20% of patients have some response in distant metastases.

The introduction of hyperfractionated radiotherapy, 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 (Kim and Leeper, 1987). Similar improvement in local disease control has been reported with a combination of hyperfractionated radiotherapy and doxorubicin, followed by debulking surgery in responsive patients. However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or improved survival. Paclitaxel has recently been tested in newly diagnosed patients and may provide some palliative benefit (Ain, 1998).

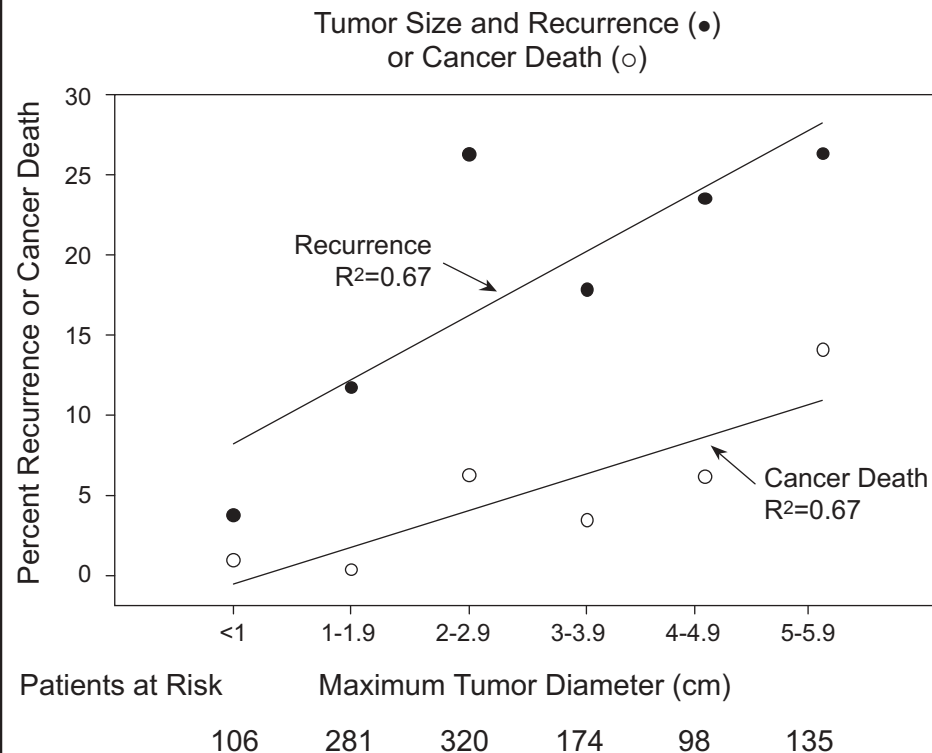
Once the diagnosis of anaplastic carcinoma is identified pathologically, the panel recognized the importance of rapid determination of the potential for local resection, since one half of all patients die from uncontrollable disease in the neck. Patients should undergo a neck CT scan and a chest x-ray. If the disease is deemed likely to be resectable, an attempt at total or near-total thyroidectomy should be made, with selective resection of all involved local or regional structures and nodes. The guidelines also recommend that patients with tumors that cannot be completely removed should, instead, receive efforts to protect their airway, including the possibility of a prophylactic tracheostomy. All patients, regardless of surgical resection, should then undergo multimodality therapy. Although optimal results have been reported with hyperfractionated radiotherapy combined with chemotherapy, the panel acknowledged the considerable toxicity associated with such treatment and the uncommon report of prolonged remission. The guidelines are silent on the question of selection of particular chemotherapeutic agent(s), either for radiosensitization or full-dose therapy related to the lack of clear evidence of efficacy. Consideration of alternative approaches to radiotherapy and chemotherapy, particularly in clinical trials, are therefore recommended.

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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