AACE/AAES MEDICAL/SURGICAL GUIDELINES FOR CLINICAL PRACTICE: MANAGEMENT OF THYROID CARCINOMA

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INTRODUCTION

The Clinical Practice Guidelines for the Management of Thyroid Carcinoma represent the third set of thyroid disease management guidelines produced by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) and, for the first time, done in collaboration with the American Association of Endocrine Surgeons (AAES). The AACE/AAES missions include heightened awareness of endocrine disorders and improved access to and quality of endocrine care. Although thyroid diseases receive little attention from the public or the medical community, they have a profound effect on the quality of life and the cost of health care.

The AACE/AAES Guidelines for the Management of Thyroid Carcinoma emphasize the importance and prevalence of thyroid cancer as a "forgotten cancer." Thyroid cancer occurs as frequently as other well-publicized cancers, such as multiple myeloma, cervical cancer, and laryngeal cancer. Approximately 17,000 new cases of thyroid cancer are diagnosed annually in the United States. Of utmost importance, many thyroid cancers are curable with appropriate treatment and follow-up. Approximately 190,000 patients are survivors of thyroid cancer.

Treatment of thyroid carcinoma remains controversial, even among the thyroid experts who produced these guidelines. These updated thyroid cancer guidelines represent a consensus of the task force, consisting of members of AACE and AAES, all of whom have contributed to our current thyroid cancer clinical management strategies.

Clinical endocrinologists must educate the public and the medical community about the prevalence and importance of thyroid disease. Furthermore, clinical endocrinologists are an important source of information about available treatment modalities for thyroid disease.

The clinical endocrinologist is best able to coordinate the comprehensive care of the patient with thyroid cancer and, when indicated, to enlist the specific expertise of other members of a multidisciplinary team. With these clinical practice guidelines, AACE and AAES hope to enhance the understanding of the currently accepted methods of managing thyroid cancer. These guidelines emphasize high-quality cost-effective care by avoiding overly aggressive treatment in patients with excellent prognoses as well as inadequate therapy for the patients at high risk of tumor recurrence and cancer-related death.

EPIDEMIOLOGY

Although thyroid nodules are extremely common, malignant lesions derived from thyroid epithelial cells are relatively rare. Clinically recognized thyroid carcinomas constitute less than 1% of all human malignant tumors. The annual incidence of thyroid cancer varies worldwide from 0.5 to 10 per 100,000 population (1). Thyroid carcinoma is as prevalent as multiple myeloma, twice as common as Hodgkin's disease, and comparable in frequency to cancers of the esophagus, larynx, mouth, and uterine cervix. It is the most common endocrine malignant lesion (90% of all endocrine cancers) and is responsible for more deaths than all other endocrine cancers combined.

The American Cancer Society estimates that 17,000 new cases of thyroid cancer are diagnosed annually in the United States and that 1,300 thyroid cancer-related deaths occur annually. Nevertheless, with appropriate treatment, the survival rate from thyroid cancer is very high. In the United States, an estimated 190,000 patients are thyroid cancer survivors, some for more than 40 years after diagnosis (1).

Carcinoma of the thyroid is usually of follicular cell origin, but medullary carcinoma arises from the parafollicular or C cells. Four distinct histologic types of follicular cell-derived cancers (FCDC) are recognized (2,3). The majority of cases are papillary, with its major subtype follicular variant (FVPTC); the other histologic types are follicular, oxyphilic or Hürthle cell, and anaplastic. Each tumor type differs substantially relative to initial mode of spread and subsequent pattern of recurrence and metastatic involvement. Although little doubt exists about the pivotal role of fine-needle aspiration (FNA) biopsy in the preoperative diagnosis of thyroid cancer, each step in the subsequent management is controversial. Unfortunately, prospective randomized controlled therapeutic trials are lacking. Therefore, we must rely on retrospective institutional or national databases. In some situations, novel therapies have been compared with inappropriate controls. Currently debated issues include the following: (*1*) the extent of primary surgical resection; (*2*) the need for and the extent of regional lymph node dissection; (*3*) the role

of postoperative radioiodine remnant ablation (RRA) in FCDC; and (*4*) the degree of suppression of thyrotropin (thyroid-stimulating hormone or TSH) needed in long-term management of FCDC.

Several prognostic factors are important for predicting the outcome in patients with thyroid cancer; this information allows appropriate counseling and selective postoperative therapy (4-9). Surgical treatment is the preferred initial management in almost all patients with thyroid cancer. Many patients with FCDC are treated with RRA. Few patients require postoperative external irradiation or chemotherapy. Although long-term survival is common, patients are at risk of tumor recurrence for decades after diagnosis. Therefore, long-term surveillance is necessary. The extent and intensity of this surveillance necessitate sound judgment and a thorough knowledge of each patient's tumor and prognosis. Appropriate surveillance may include radiologic and radionuclide imaging and measurement of thyroid-specific tumor markers. Optimal care of patients with thyroid cancer may require a multidisciplinary team, including physicians with special expertise in endocrinology, surgery, pathology, nuclear medicine, radiation oncology, medical oncology, clinical chemistry, and diagnostic radiology.

DIAGNOSIS

At the time of initial assessment, most patients with thyroid cancer have a palpable neck mass, either a primary intrathyroidal tumor or metastatic regional lymphadenopathy. In some patients, however, the tumor may be clinically occult, and the impalpable lesion may first be recognized on a high-resolution neck image or at the time of surgical intervention for presumed benign thyroid disease. In patients with a family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN) type II syndromes, the finding of a *RET* proto-oncogene mutation or abnormal basal or stimulated calcitonin level may necessitate prophylactic thyroidectomy in a patient who may prove to have early MTC or C-cell hyperplasia. Unfortunately, even thorough history taking and physical examination rarely allow the definitive diagnosis of thyroid cancer. The diagnosis of thyroid cancer necessitates cytologic or histologic confirmation. FNA biopsy is the most cost-effective method of distinguishing benign from malignant thyroid nodules preoperatively (4,10). The diagnosis of thyroid cancer must be substantiated by careful pathologic examination of surgically excised thyroid tissue. This verification is particularly important in cases of cellular follicular lesions described by cytologists as "suspicious" for follicular or Hürthle cell neoplasm (also known as follicular neoplasms or microfollicular lesions). For accurate diagnosis of follicular carcinoma (including the Hürthle cell variant), one must clearly demonstrate tumor invasion through the capsule of the nodule or tumor invasion of blood vessels (angioinvasion). This process necessitates multiple serial sections through the excised paraffin-fixed specimens and careful evaluation for the presence or absence of such microinvasion. Intraoperative frozen section is often inadequate for this purpose (11,12).

Papillary thyroid carcinoma (PTC) constitutes 75 to 80% of cases of clinically recognized thyroid cancer and can often be diagnosed with confidence by FNA biopsy (13). Indeed, some authorities believe that the characteristic nuclear abnormalities diagnostic for PTC are optimally seen in cytologic preparations from FNA biopsy specimens, rather than in frozen sections or in paraffin-embedded histologic material. MTC may be readily diagnosed by FNA biopsy, but in equivocal cases, amyloid staining with Congo red, immunoperoxidase labeling of intracytoplasmic calcitonin, or serum calcitonin measurements yield a definitive preoperative diagnosis (14). Unfortunately, diagnosis of follicular cancer by cytologic, rather than histologic, analysis is rarely possible.

Anaplastic (undifferentiated) thyroid carcinoma is usually diagnosed by FNA biopsy, but occasionally it may be difficult to distinguish from carcinoma metastatic to the thyroid. Cytokeratin may be the most useful epithelial marker for anaplastic thyroid carcinoma (15). Although most anaplastic thyroid carcinomas do not stain for thyroglobulin (Tg), positive Tg immunostaining confirms a thyroidal origin. Thyroid lymphoma may be difficult to diagnose by FNA (16), but flow cytometry (confirming the clonal origin of the tumor) and lymphocyte nuclear atypia often help distinguish the lymphocyte population from that of Hashimoto's thyroiditis (17). Occasionally, verification may necessitate open biopsy in conjunction with specific immunostaining for clonal B- and T-cell populations.

PRIMARY TREATMENT

Papillary Thyroid Carcinoma

No prospective clinical trials have clearly determined the "best treatment" of patients with PTC. In most cases, a preoperative diagnosis of PTC established by FNA allows appropriate surgical planning. Total ipsilateral thyroid lobectomy is generally thought to be the minimal surgical procedure for a unilateral, possibly malignant thyroid nodule. Minimal PTCs are defined as cancers smaller than 1 cm, which do not extend beyond the thyroid capsule and are not metastatic or angioinvasive. Patients with such cancers have a death rate of about 0.1% and a recurrence rate of approximately 5% (3). Unilateral total lobectomy may be an appropriate definitive procedure for patients with minimal thyroid cancers (18-20). A total lobectomy is recommended for suspicious thyroid nodules, in an effort to avoid the possibility of a subsequent difficult or dangerous completion lobectomy if the final diagnosis is a malignant lesion.

Most surgeons agree that total or near-total thyroidectomy is the preferred operation for high-risk patients with PTC—as defined by the AMES (age of patient, presence of distant metastatic lesions, and extent and size of the primary cancer), AGES (patient age and tumor grade, extent, and size), TNM (tumor characteristics, lymph node

involvement, and distant metastatic lesions), EORTC (European Organization for Research and Treatment of Cancer), or MACIS (metastatic lesions, patient age, completeness of resection, invasion, and size of tumor) classification system (4-9,21). A total or near-total thyroidectomy is also recommended in a patient with PTC when bilateral nodules are present, when cancer is bilateral, when the primary tumor extends beyond the thyroid capsule, or when local or distant metastatic disease is present. For several reasons, however, opinions differ about the extent of thyroid resection for patients with low-risk PTC. Most of these patients have an excellent prognosis as long as gross tumor is completely resected. Some surgeons advocate less than a complete thyroidectomy to avoid hypoparathyroidism and minimize the risk of damage to the recurrent laryngeal nerves. Demonstration of a survival advantage of bilateral in comparison with unilateral resection in low-risk patients is difficult. The risk of hypoparathyroidism and recurrent laryngeal nerve injury is less than 2% when thyroidectomy is performed by experienced thyroid surgeons, but it is higher when the procedure is done by less-experienced surgeons. Although the incidence of recurrent laryngeal nerve palsy per nerve at risk is similar for unilateral versus bilateral procedures, postoperative permanent hypoparathyroidism rarely is a complication of unilateral lobectomy. The following arguments are advanced in favor of total or near-total thyroidectomy. PTC is often multifocal and may spread throughout the thyroid by lymphatic drainage. Total or near-total thyroidectomy facilitates the postoperative use of ^{131}I to ablate residual thyroid tissue and to identify and treat residual or distant tumor. After total thyroidectomy, Tg is a more sensitive indicator of residual disease. Many retrospective studies have reported a lower recurrence rate and tumor-free survival rate (2,7,18,20) after bilateral than after unilateral resection. Treatment strategies in low-risk papillary carcinoma are based on retrospective analysis. A well-designed prospective study is necessary to determine the optimal therapy based on cost-to-benefit analyses, risk, recurrence rates, and survival.

If the parathyroid glands cannot be preserved during the surgical procedure, they should be removed, biopsies should be obtained to confirm the presence of parathyroid tissue, and parathyroid tissue should be autotransplanted into muscle. Some surgeons routinely recommend near-total thyroidectomy, leaving about 1 g of thyroid tissue contralateral to the thyroid cancer to protect the upper parathyroid gland and recurrent laryngeal nerve. This strategy has merit when the surgeon is concerned about the viability of the other parathyroid glands but seems illogical when minimal manipulation of the recurrent laryngeal nerve and other parathyroid glands is necessary. Lymph node metastatic lesions are present in about 40% of adult patients with PTC; complete lymphadenectomy of involved nodes is recommended (6). In children and young adults, clinical node involvement is more common. Nodal metastatic lesions increase the risk for subsequent nodal recurrences but have little effect on survival. Surgeons should remove all enlarged lymph nodes in the central and lateral neck areas. In the central neck, removal is essential because reoperations in this area are more difficult and are associated with a higher risk of complications. When enlarged nodes are identified in the lateral aspect of the neck, most surgeons perform an ipsilateral functional (modified radical neck) dissection and remove all the perijugular nodes from the clavicle to the hyoid, including the nodes along the spinal accessory nerve. During this operation, the spinal accessory nerve, internal jugular vein, cervical sensory nerves, and sternocleidomastoid muscle should be preserved. Prophylactic lateral neck dissection is not recommended, and radical neck dissections that result in loss of function are rarely indicated for patients with PTC unless direct muscle invasion is present.

Follicular or Hürthle Cell Carcinoma

Most follicular and Hürthle cell neoplasms are large (2- to 5-cm), relatively soft, solitary thyroid nodules. Typically, FNA cytologic findings are reported as "indeterminate or suspicious for follicular or Hürthle cell neoplasm" (13). About 80% of follicular and Hürthle cell neoplasms are benign; larger follicular or Hürthle cell neoplasms are more likely to be malignant, especially in men and patients older than age 50 years. Unfortunately, follicular adenomas and carcinomas usually cannot be distinguished at the time of surgical intervention. Therefore, most surgeons recommend a total thyroid lobectomy with isthmusectomy for "follicular or Hürthle cell neoplasms." When the lesion is benign, no further therapy is needed. When the tumor is malignant, completion (total) thyroidectomy may be indicated to facilitate subsequent radioactive iodine (RAI) scanning and therapy. Some clinicians use RAI to ablate the residual lobe, inasmuch as follicular carcinomas are rarely bilateral. When follicular carcinoma is minimally invasive and characterized only by limited capsular invasion, lobectomy is likely to provide definitive therapy. When more extensive capsular or vascular invasion is present, completion total thyroidectomy or RAI ablation is warranted. Risk-group classification (AMES, AGES, TNM, EORTC, or MACIS) is also considered by many surgeons as a criterion before completion thyroidectomy is recommended (4-9). The risk of reoperation is minimal because the contralateral recurrent laryngeal nerve and parathyroid glands are in an undissected field. Before reoperation is considered, normal recurrent laryngeal nerve function should be demonstrated by direct laryngoscopy, and the pathology specimen should be carefully reviewed to determine whether any parathyroid glands have been removed.

Ipsilateral lymph node metastatic lesions occur in only about 10% of patients with follicular thyroid cancer (FTC) and in about 25% of patients with Hürthle cell cancer (22). When lymphadenopathy is extensive in a patient with a follicular neoplasm as determined by FNA cytology, the tumor is usually a follicular variant of PTC. Enlarged lymph nodes in the central neck area should be removed. A functional lateral neck dissection is indicated for patients with clinically palpable nodes.

POSTOPERATIVE STAGING

During the past decade, the International Union Against Cancer (Union Internationale Contre le Cancer or UICC) and the American Joint Committee on Cancer (AJCC) have agreed on a staging system for thyroid carcinoma (21). The AJCC classification is based on the TNM system, which assesses the following three components: the size and extent of the primary tumor (T), the presence or absence of regional lymph node metastatic involvement (N), and the presence or absence of distant metastatic lesions (M) (Table 1). These three categories are further subdivided numerically; thus, progressive increase in tumor size and involvement can be indicated. The TNM classification may be either clinical (cTNM), based on evidence (including FNA biopsy) acquired before treatment, or pathologic (pTNM), based on available intraoperative and surgical pathologic data.

The postoperative TNM classification is preferable because the tumor can be categorized histologically and can be precisely measured, and the extrathyroid invasion can be unequivocally demonstrated. Characteristics of TNM staging are reviewed in Table 1. Typically, the primary tumor status is defined on the basis of the size of the primary lesion (T1, greatest diameter 1 cm or smaller; T2, larger than 1 cm but not larger than 4 cm; T3, larger than 4 cm) or by direct (extrathyroid) extension or invasion through the thyroid capsule (T4). Because a thyroid cancer may have 4 degrees of T, 2 degrees of N, and 2 degrees of M, 16 different TNM categories are possible. The AJCC has condensed these categories into four convenient TNM stages (Table 1). In contrast to other head and neck tumors, which are staged exclusively by anatomic characteristics, thyroid cancer staging is unique in that both the histologic diagnosis and the age of the patient are included as factors because of their prognostic importance.

On the basis of this staging scheme, all young patients (younger than 45 years of age) with FCDC have stage I disease unless they have distant metastatic lesions—in which circumstance, stage II disease is present. Older patients (45 years old or older) with node-negative papillary or follicular microcarcinoma (T1, N0, M0) have stage I disease. Tumors between 1.1 and 4.0 cm are stage II, and either nodal involvement or extrathyroid invasion in older patients with FCDC is assigned a stage III classification. For MTC, the scheme is similar in that microcarcinoma is stage I and node-positive results are stage III; however, no age distinction exists for MTC, and the presence of local (extrathyroid) invasion is defined as stage II. Both for MTC and for older patients with FCDC, stage IV denotes the presence of distant metastatic involvement. Independent of tumor extent, all patients with anaplastic thyroid carcinoma are considered to have stage IV disease.

The pTNM system is the most widely accepted classification used to assess the extent of disease for staging of thyroid cancer and is recommended by AACE (4). It is the standard system used by US hospitals in their reporting of new cases of thyroid carcinoma. In effect, it is a "shorthand notation" for describing the clinical extent of thyroid carcinoma. It does not, however, provide all the information that a clinician may need for classifying an individual patient in a particular risk group. An improved, and more refined, risk assignment may be achieved by considering additional prognostic indicators demonstrated to be independent predictors of outcome in rigorous multivariate analyses.

RISK-GROUP ASSIGNMENT

The most important risk factors for FCDC and MTC tumor recurrence and cause-specific mortality are age at time of initial assessment, tumor size, presence of extrathyroid invasion, and presence of distant metastatic lesions (6). Lymph node metastatic lesions at the time of initial examination do not increase the risk of death from PTC but do increase the risk of local and regional recurrences (22). Although nodal metastatic lesions are uncommon in FTC, their presence may indicate a worse prognosis. Initial nodal metastatic disease in MTC predicts a higher risk of recurrence and death. Tumor grade is an established risk factor in PTC but is seldom assessed on routine postoperative histologic examination (23). For FTC, no widely accepted grading system has been developed. Minimally invasive FTC characterized by capsular invasion alone rarely spreads or causes death. The prognosis is slightly worse when, at most, a few blood vessels are invaded. FTC with extensive vascular invasion denotes a much worse prognosis and often demonstrates

Table 1
Staging System for Thyroid Carcinoma
Established by the American Joint Committee on Cancer

Stage	Papillary or follicular		Medullary, any age	Anaplastic, any age
	Age <45 yr	Age ≥45 yr		
I	M0	T1	T1	…
II	M1	T2-3	T2-4	…
III	…	T4 or N1	N1	…
IV	…	M1	M1	Any

hematogenous spread to the lungs and bone. Poorly differentiated FTC tumors are often widely invasive and are associated with a poor prognosis (9).

Several rare thyroid cancer histologic subtypes may indicate a worse prognosis. These include the Hürthle cell (oxyphilic), tall cell, and columnar variants of PTC and possibly the diffuse sclerosing variant (24). The oxyphilic variant of FTC is associated with a greater risk of nodal recurrence; poorly differentiated "insular" FTC is associated with a significantly increased risk of death. DNA aneuploidy does not have prognostic value in PTC or typical FTC but may predict significantly increased mortality in oxyphilic FTC (25). Complete tumor resection (absence of gross residual tumor) of MTC and FCDC predicts a more favorable outcome (25,26). Lastly, delay in instituting therapy after diagnosis of cancer may adversely affect survival in patients with FCDC (7).

During the past 2 decades, knowledge of these relevant prognostic factors has led to several staging or scoring systems that have been derived from extensive analyses and facilitate the classification of patients with FCDC into categories at low, intermediate, or high risk of cause-specific mortality. Because most cancer-related deaths are mediated through biologically significant recurrent events at local or distant sites, these schemes also provide data relevant to tumor recurrence rates in patients who have undergone complete resection of their primary tumors (27).

The variables used in the creation of the original prognostic index system (5), devised in 1979 by the EORTC, are contrasted in Table 2 with those used in six other schemes determined at US centers during the period 1987 through 1995. Of note, all these schemes include both extrathyroid invasion and distant metastatic involvement. Most schemes include patient age and tumor size (6,22,23). The majority take histologic type into consideration. A few consider nodal metastatic lesions (6,7,9) and patient sex (6). Some include histologic grade (9,23) and the presence of multiple (more than three) tumors (28). Only one scheme includes the presence of gross residual disease after primary surgical resection.

Use of such schemes facilitates the classification of an individual patient with FCDC into a particular risk-group category, based entirely on data readily available within days after the primary neck exploration. Such classifications allow fairly accurate identification of the majority (80 to 85%) of patients with FCDC as being at low risk of cause-specific mortality (27,29). Adjuvant treatment and close follow-up can then be targeted to high-risk patients, whereas a less intensive interventional approach can be used in low-risk patients (Table 2).

ADJUVANT THERAPY

Thyroid Hormone

The administration of supraphysiologic doses of thyroid hormone to suppress serum TSH in patients with FCDC has been a mainstay of therapy for more than 40 years (30,31). Growth of FCDC cells depends on TSH; suppression of endogenous TSH is thought to deprive these cells of an important growth-promoting influence. Traditionally, the goal of levothyroxine therapy has been complete suppression of pituitary secretion of TSH, as indicated by undetectable levels of serum TSH when measured in sensitive immunometric assays or, formerly, by the absence of a serum TSH increase in response to intravenous or oral administration of thyrotropin-releasing hormone. The efficacy of such suppressive therapy, however, is unproven because no prospective controlled trials have been reported.

In retrospective univariate analyses, levothyroxine therapy apparently decreases cancer-related death rates among patients with PTC. In some series, however, this survival effect has been confined to patients beyond 50 years of age, whereas in other studies, the survival advantage is insignificant when patients with PTC are stratified on the basis of other risk factors. Many series have reported reduced rates of tumor recurrence, both in PTC and in FTC, with suppressive therapy (31). Although patients with MTC require thyroid hormone replacement therapy after bilateral thyroidectomy, C cells are not TSH dependent and thyroid hormone suppressive therapy is unnecessary.

Meticulous titration of the level of TSH suppression is now possible because sensitive TSH assays are widely available (24,32). Generally, we advocate the use of a third-generation TSH assay, which can measure serum TSH down to 0.01 μIU/mL. A basal serum level of <0.1 μIU/mL has typically been considered equivalent to a nonresponse of TSH in a thyrotropin-releasing hormone stimulation test, previously considered the hallmark for adequate TSH suppression in FCDC (33,34).

Long-term levothyroxine suppressive therapy may have adverse effects on bone and the heart, including accelerated bone turnover, osteoporosis, and atrial fibrillation (32,35,35a). Consequently, many experts maintain that long-term complete TSH suppression (<0.01 to <0.1 μIU/mL) should be reserved for higher risk patients (33,34), particularly those patients with FCDC who are at high risk for recurrence or mortality and those with persistent or recurrent carcinoma that cannot be eradicated. In contrast, most clinicians believe a lesser degree of TSH suppression will suffice for most patients with PTC classified as low risk by prognostic scoring systems. In these patients, the TSH goal would be in the range of 0.1 to 0.4 μIU/mL. No published prospective data, however, have addressed this important issue. This situation underscores the role of good clinical judgment and individualization of levothyroxine treatment for patients with thyroid cancer.

Radioiodine Remnant Ablation

Many patients with FCDC receive RAI (^{131}I) to ablate residual thyroid tissue postoperatively (RRA) (36). RRA is defined as "the destruction of residual macroscopically normal thyroid tissue after surgical thyroidectomy." RRA is used as an adjunct to surgical treatment when the primary FCDC has been completely resected. This technique

Table 2
Components of Prognostic Schemes Used for Defining Risk-Group Categories in Patients With FCDC*

Prognostic variable	Staging or scoring systems†						
	EORTC (1979)	AGES (1987)	AMES (1988)	U of C (1990)	MACIS (1993)	OSU (1994)	MSKCC (1995)
Patient factors							
Age	X	X	X	…	X	…	X
Sex	X	…	X	…	…	…	…
Tumor factors							
Size	…	X	X	X	X	X	X
Multicentricity	…	…	…	…	…	X	…
Histologic grade	…	X	…	…	…	…	X
Histologic type	X	‡	X	…	‡	…	X
Extrathyroid invasion	X	X	X	X	X	X	X
Nodal metastatic lesion	…	…	…	X	…	X	X
Distant metastatic lesion	X	X	X	X	X	X	X
Operative factors							
Incomplete resection	…	…	…	…	X	…	…

*FCDC = follicular cell-derived cancer; X = variable used in defining risk group; … = variable not used.
†EORTC = European Organization for Research and Treatment of Cancer; AGES = patient age and tumor grade, extent, and size; AMES = patient age, presence of distant metastatic lesions, and extent and size of primary cancer; U of C = University of Chicago; MACIS = metastatic lesions, patient age, completeness of resection, invasion, and size of tumor; OSU = Ohio State University; MSKCC = Memorial Sloan-Kettering Cancer Center.
‡Schemes devised only for papillary thyroid carcinoma.

is contrasted with RAI therapy, in which larger doses of ^{131}I are administered in an attempt to destroy persistent neck disease or distant metastatic lesions.

Proponents of RRA believe that this therapy has three potential advantages (37): (*1*) ^{131}I may destroy microscopic cancer cells within the thyroid remnant because of their proximity to the remaining normal thyroid tissue; (*2*) subsequent detection of persistent or recurrent disease (particularly in the neck) by radioiodine scanning is facilitated by the destruction of remaining normal tissue; and (*3*) after RRA, the sensitivity of serum Tg measurements is improved during follow-up. Improved efficacy of Tg measurements has convinced some clinicians to use RRA in low-risk patients with FCDC. Other investigators, however, do not use RRA in these low-risk patients because of lack of evidence of improved outcome. The issue of RRA in low-risk patients remains unsettled; a case-by-case decision is recommended, guided by clinical judgment and experience.

The standard ^{131}I dose used in the past for RRA was from 75 to 150 mCi (2,775 to 5,550 MBq). In recent years, some US centers have used a low-dose regimen of 25 to 29.9 mCi (925 to 1,110 MBq), especially if the amount of thyroid remnant tissue was small. The low-dose regimen is less expensive, results in a lower dose of whole-body irradiation, and does not necessitate hospitalization (38). In some states, however, newer guidelines from the Nuclear Regulatory Commission permit the use of higher outpatient doses of radioiodine. The mean exposure with whole-body irradiation after administration of ablative RAI has been estimated to be 6.1 rem for 30 mCi (1,110 MBq), 10.2 rem for 50 mCi (1,850 MBq), and 12.2 rem for 60 mCi (2,220 MBq). Currently, no consensus exists about the most appropriate dose of RAI for remnant ablation.

LONG-TERM FOLLOW-UP

Diagnostic Scanning

Conventional Protocol

For whole-body scanning (WBS) with RAI, an increased serum TSH level (generally, >25 μIU/mL) is necessary to allow FCDC cells to accumulate the radioiodine. This state is usually accomplished by the withdrawal of thyroid hormone therapy (4,37). Levothyroxine is discontinued for at least 6 weeks before scanning; triiodothyronine (T_3), 25 μg two or three times a day, is given during the first 4 weeks of levothyroxine withdrawal to minimize the duration of hypothyroidism. Lower doses are selected in elderly patients and in those with underlying heart disease. Administration of T_3 is then discontinued for 2 weeks. A low-iodine diet is consumed for

2 to 4 weeks before radioiodine scanning. After a total or near-total thyroidectomy, more than 90% of patients will achieve a serum TSH concentration of >25 μIU/mL, the necessary level for optimal scanning. ^{131}I WBS is generally performed 48 to 72 hours after the administration of 2 to 5 mCi of ^{131}I. Serum TSH and Tg should be measured before administration of RAI. Symptoms of hypothyroidism, which may be unpleasant and severe, remain the major drawback of this protocol. Patient adherence may be poor when frequent withdrawal of thyroid hormone therapy is necessary. Thyroid hormone withdrawal may be contraindicated in patients with severe pulmonary or cardiovascular disease.

Results of WBS determine radioiodine therapy. Ablative doses of RAI (30 to 150 mCi) are given to patients with functioning remnants in the thyroid bed. Higher doses are administered when metastatic disease is demonstrated. Pregnancy must be excluded before ^{131}I is given. A posttreatment scan, which may reveal additional sites of disease, is commonly performed 4 to 10 days after the therapeutic dose of radioiodine has been administered. Thyroid hormone therapy is restarted after treatment. Many clinicians resume treatment with levothyroxine 2 to 5 days after administration of RAI. Some physicians administer T_3 for 10 days to accelerate the return to euthyroidism and minimize the duration of high serum TSH levels.

Recombinant Thyrotropin

Recombinant human TSH (rhTSH) has been approved by the US Food and Drug Administration for use in radioiodine scanning of patients with FCDC (39-41). rhTSH is a highly purified recombinant form of human TSH, synthesized in a Chinese hamster ovary cell line. A glycosylation pattern different from native human TSH accounts for its long half-life.

rhTSH stimulates radioiodine uptake in normal and abnormal residual thyroid tissue, and it stimulates production of Tg by normal and abnormal thyroid tissue. Two phase III, peer-reviewed clinical trials demonstrated the utility of rhTSH in the diagnosis of thyroid cancer (41,42). In these studies, 48-hour ^{131}I WBS results obtained after administration of rhTSH were compared with similar scans after withdrawal of levothyroxine therapy. The following is a summary of these results.

^{131}I WBS results were concordant between rhTSH-stimulated and levothyroxine-withdrawal phases in 89% of patients; of the discordant results, 8% of scans were superior after levothyroxine withdrawal, whereas 3% of scans were superior after stimulation with rhTSH (difference not significant). In both groups, however, many patients had negative scans that were not informative. In 48 patients with positive scans, rhTSH-stimulated and levothyroxine-withdrawal scans were concordant in 75%; the withdrawal scan was superior in 19%, and the rhTSH scan was superior in 6% (differences not significant). Of note, very few scans demonstrated radioiodine uptake outside the neck.

Serum Tg is dependent on serum TSH. Serum Tg declines when the TSH level is suppressed, and it increases when the TSH concentration rises. On the basis of a serum Tg level of 2 ng/mL or more, thyroid tissue or cancer was detected during levothyroxine therapy in 22%, after rhTSH stimulation in 52%, and after levothyroxine withdrawal in 56% of patients with disease or tissue limited to the thyroid bed and in 80%, 100%, and 100% of patients, respectively, with metastatic disease (42). The addition of Tg measurement to radioiodine scanning enhanced the sensitivity. The combination of rhTSH WBS plus rhTSH Tg testing identified 100% of 32 patients with metastatic disease. The investigators concluded that rhTSH is a safe and effective means of stimulating ^{131}I uptake and serum Tg levels in patients undergoing assessment for recurrence of thyroid cancer. Symptoms of hypothyroidism did not occur in the rhTSH group.

***Clinical Applications.*—**Current clinical applications for rhTSH include the following: as an alternative to the traditional levothyroxine-withdrawal protocol; in patients with demonstrated inability to generate endogenous TSH secretion attributable to hypothalamic or pituitary disease; for patients who are unable or unwilling to undergo levothyroxine-withdrawal testing; to enhance sensitivity of Tg in thyroid cancer follow-up; and in patients in whom hypothyroidism is relatively contraindicated because of severe pulmonary or cardiac disease (43,44). On the basis of clinical trials, adverse reactions include nausea in 10.5%, headaches in 7.3%, asthenia in 3.4%, vomiting in 2.1%, dizziness or paresthesias in 1.6%, and chills, fever, "flu," and other nonspecific symptoms in 1%. Mild reactions of hypersensitivity consisting of urticaria and rash in <1% have been reported. These side effects were transient and never serious. Anti-TSH antibodies were not detected (39,42).

***rhTSH Protocol.*—**In our proposed protocol for TSH-mediated monitoring, the patient continues levothyroxine therapy without interruption (42). rhTSH, 0.9 mg, is administered intramuscularly on 2 consecutive days. On the third day, 4 mCi of ^{131}I is administered, and 48 hours later, WBS is performed. Serum TSH and Tg levels are measured before injection and on the day of scanning. This protocol involves 5 days and is best begun on Monday and concluded on Friday, although other schedules can be arranged as well (44).

The two-dose regimen consisting of 0.9 mg of rhTSH intramuscularly each day for 2 days is most convenient for the patient. Results were comparable to those with a three-dose regimen in phase III trials.

Thyroglobulin

Thyroid tissue is the only source of circulating Tg. Serum Tg levels may be high in thyrotoxicosis, thyroiditis, iodine deficiency, and benign thyroid adenomas as well as in thyroid cancer (45,46). Therefore, it is not a screening test for thyroid cancer; as a product of the thyroid follicular cells, Tg levels are not increased in medullary or anaplastic thyroid carcinomas. Serum Tg is a highly

specific tumor marker for differentiated thyroid cancer and has a pivotal role in follow-up of patients with such cancers. After bilateral thyroidectomy and successful radioiodine ablation, serum Tg should be undetectable (generally, <2 ng/mL). After a unilateral lobectomy, serum Tg is usually less than 10 ng/mL during thyroid hormone therapy in the absence of metastatic disease (47). Because some thyroid cancers are poor secretors of Tg, a preoperative Tg measurement is helpful for determining whether the patient's thyroid cancer is a secretor or not. Storage of a sample of Tg each time it is assayed may also be valuable, in order to compare previous values with current values—especially when different Tg assays are used (46,48). Tg stores well when frozen. After successful total thyroidectomy and ^{131}I therapy for thyroid cancer, normalization of Tg levels may take several months.

Serum Tg is a particularly useful tumor marker after bilateral thyroidectomy or thyroidectomy plus ablation. Tg production and concentration depend on the serum TSH concentration. An undetectable serum Tg when the serum TSH level is high excludes residual or metastatic cancer in more than 99% of cases. In contrast, a high serum Tg level when the TSH concentration is suppressed indicates residual abnormal thyroid tissue, although it cannot distinguish nodular disease from a malignant lesion. Unfortunately, a low serum Tg concentration during thyroid hormone suppression does not exclude metastatic disease. Therefore, serum Tg concentrations are most helpful in patients with high-risk FCDC when the serum TSH level is high, after either withdrawal of levothyroxine or administration of rhTSH injections. Use of rhTSH may be helpful in patients who do not respond to withdrawal from levothyroxine by raising endogenous TSH adequately, such as those with pituitary failure (49). Unfortunately, serum Tg assays are not well standardized. Detection limits must be verified for the specific assay used. Inconsistencies between assays account for some of the variations in Tg values; thus, clinical decision making is complicated.

When Tg antibodies (TgAb) are present, serum Tg measurements are generally unreliable. Falsely high or low readings may occur. Therefore, all Tg samples must be routinely screened for anti-TgAb, and the responsible laboratory must inform the clinician when such antibodies are present in concentrations sufficient to invalidate the Tg measurement. TgAb may diminish after months or years; hence, their current presence does not preclude subsequent Tg measurements. In some studies, persistence of TgAb has been correlated with residual tumor when all residual thyroid tissue has been ablated. Currently, no commercial assay is available that circumvents the difficulties of TgAb. Immunoassays that measure both free and antibody-bound Tg are preferred to immunoassay methods that measure only free Tg in the patient with detectable TgAb (50). The measurement of circulating Tg messenger RNA (mRNA) may help overcome the limitations of the currently available Tg assays. Detection of circulating Tg mRNA is a more sensitive marker of residual thyroid tissue or cancer than immunoassay for serum Tg (51). At this time, however, no Tg mRNA assay is sufficiently quantitative for widespread use.

Some investigators suggest that routine ^{131}I WBS may be uninformative in most patients who have undergone thyroidectomy and radioiodine ablation. Measurement of Tg after thyroid hormone withdrawal, using 10 ng/mL as a cutoff, has been suggested to predict those patients in whom scanning is likely to disclose residual disease (52).

An approach to the use of rhTSH in the assessment and management of patients with thyroid cancer after thyroidectomy during levothyroxine suppression therapy includes monitoring of serum Tg levels. When the serum Tg is >5 ng/mL while the patient is receiving levothyroxine suppression therapy, WBS is done after levothyroxine withdrawal. If serum Tg is 2 to 5 ng/mL, rhTSH is given to evaluate the Tg response. When the Tg level is <2 ng/mL during levothyroxine suppression, the high-risk patient or patient less than 2 years after surgical treatment should be retested by using rhTSH stimulation for scanning and Tg measurement as well as localization studies, such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) scans of the neck and superior mediastinum. The low-risk patient or patient beyond 2 years after surgical treatment should undergo retesting in 1 year.

For patients retested with use of rhTSH whose serum Tg is <2 ng/mL and whose Tg level has increased <1 ng/mL since a previous measurement, retesting is done in 1 year. When rhTSH-stimulated Tg is 2 ng/mL or is <2 ng/mL but is ≥1 ng/mL higher than previously, the patient risk category determines further action. High-risk patients and those whose rhTSH-stimulated Tg is 10 ng/mL or higher are studied by WBS after withdrawal of levothyroxine therapy. ^{131}I treatment follows, if indicated by the WBS findings. Low-risk patients, after undergoing an initial 1-year postoperative levothyroxine withdrawal scan and determination of the Tg level, may be studied with rhTSH-stimulated Tg and WBS testing and, if results are negative, may be retested in 1 to 3 years. With positive results of rhTSH-stimulated WBS, levothyroxine withdrawal for ^{131}I treatment is appropriate (40).

Although ^{131}I scanning seems to be less sensitive after administration of rhTSH than after thyroid hormone withdrawal, the combined use of scanning and measurements of serum Tg improves the sensitivity of rhTSH monitoring, and use of rhTSH avoids the severe, transient hypothyroidism that occurs with thyroid hormone withdrawal (53).

Most patients with FCDC undergo follow-up during the first 1 to 3 postoperative years with a combination of Tg measurements and appropriate scanning. Some physicians monitor serum Tg during thyroid hormone suppressive therapy in patients with FCDC after unilateral or bilateral thyroidectomy, with or without RRA. Patients who have had a unilateral procedure and those who have not undergone ablation may be more difficult to assess. Nonetheless, serum Tg levels >10 ng/mL in these patients indicate the need for further diagnostic testing (54). Many

clinicians advocate high-resolution ultrasonography of the neck or thyroid as an adjunct to Tg measurements, particularly in patients with suspicious clinical findings, those with a high risk of recurrence, and TgAb-positive patients (55,56).

Imaging

Radioiodine uptake and retention are specific for normal or neoplastic thyroid tissue. Identification of radioiodine-avid tumor tissue allows for subsequent ^{131}I therapy. Scans are most useful when little normal thyroid tissue remains. If large amounts of normal thyroid tissue are present, the serum TSH level will not be sufficiently high to allow radioiodine uptake of tumor tissue. In addition, when the radioiodine uptake is high in the neck, a "starburst" pattern may occur and prevent visualization of tumor elsewhere. Current scanning methods, however, have minimized this latter problem.

Typically, WBS is performed with use of 2 to 5 mCi (74 to 185 MBq) of ^{131}I, and quantitative uptakes are measured at 48 and 72 hours. Although some investigators prefer to use larger scanning doses, most metastatic lesions amenable to RAI therapy are unlikely to be missed in an athyreotic patient by using diagnostic doses of 2 to 3 mCi (74 to 111 MBq) of ^{131}I (57). Larger ^{131}I scanning doses may result in thyroid "stunning," whereby the tissues concentrating ^{131}I are sufficiently harmed by the scanning dose such that subsequent uptake of therapeutic RAI may be adversely diminished (58).

Single-photon emission computed tomography (SPECT) whole-body imaging with ^{123}I doses of 1 mCi or more that are performed within 24 hours after the administration of ^{123}I may prove to be an effective alternative to pretherapeutic WBS with ^{131}I (59). With use of ^{123}I, stunning is avoided. Relatively high ^{123}I doses and the resolution of SPECT imaging enhance the detection of metastatic lesions with rapid iodine turnover. SPECT imaging helps distinguish upper bowel from lower lung radioactivity—a distinction that may be particularly important on 24-hour imaging studies, in light of the short half-life of ^{123}I.

Usually, WBS is performed 6 to 8 weeks after total thyroidectomy. This schedule may vary if a substantial increase in serum TSH is established sooner. The efficacy of RRA can be demonstrated 3 to 6 months after RRA, but many clinicians defer repeated WBS for 12 months, particularly when the risk of metastatic involvement is low. After a negative scan is achieved, repeated scanning may be triggered by a considerably increased serum Tg level or clinical findings suggestive of potential tumor recurrence. WBS should be repeated 3 to 10 days after an ablative dose of ^{131}I. Additional information is obtained in approximately 10% of such scans. Periodic scanning may be advised in high-risk patients.

Most PTC and MTC recurrences are in the neck. Therefore, initial targeted imaging should be directed to the central and lateral aspects of the neck. High-resolution CT and MRI are commonly used for this purpose; however, medical centers with expertise in the use of real-time high-frequency ultrasonography recommend this procedure as the initial imaging modality of choice (60). High-resolution ultrasonography can reveal abnormalities down to 1 mm, is relatively inexpensive, and is convenient to perform in the office. With suspicious thyroid bed nodules or cervical lymph nodes, biopsies can be obtained under ultrasound guidance, but this procedure necessitates additional training and experience for safe procurement of tissue for diagnosis.

When radioiodine scanning and neck ultrasonography are unrevealing in a patient with FCDC who has high serum Tg levels, additional imaging studies are necessary. In this circumstance, pulmonary metastatic lesions are common and are occasionally evident on a chest roentgenogram. More often, the metastatic growths are micronodular and may be visualized only by high-resolution helical or spiral CT scanning (61). When FCDC is metastatic to bone, the metastatic lesions are always lytic. A positive bone scan is helpful, but isotopic bone scans may be negative in as many as 40% of patients with FCDC metastatic to bone. Therefore, a conventional radiographic bone survey, or CT or MRI, may be necessary to localize the bony metastatic lesions. Intracranial and small mediastinal metastatic lesions are detected with CT or MRI.

Intra-abdominal metastatic lesions are uncommon but can be revealed with ultrasonography, CT, and MRI. If the source of a high Tg level remains uncertain, additional imaging studies should be considered. Many clinicians perform a levothyroxine-withdrawal scan after administration of therapeutic doses of ^{131}I (100 to 300 mCi), particularly when the only recent radioiodine scan has been performed with low doses of ^{131}I or ^{123}I. Intracranial and spinal metastatic lesions should be excluded before withdrawal of thyroid hormone in these patients, inasmuch as more rapid tumor growth may occur when the serum TSH level is increased. Additional isotopic scans may be of benefit: WBS with ^{201}Tl (62), ^{99m}Tc sestamibi (63), or tetrofosmin (64), ^{111}In pentetreotide, and positron emission tomographic (PET) scanning with fluorodeoxyglucose (65). Thyroid hormone withdrawal is not necessary before performance of these scans. Most clinicians favor sestamibi over ^{201}Tl, particularly when SPECT imaging is available. Tetrofosmin is a promising new agent that may prove comparable to sestamibi, but additional studies are necessary. Labeled pentetreotide, which is generally considered specific for MTC, may also be used for imaging of FCDC, especially the oxyphil variant (66). Image quality and resolution with fluorodeoxyglucose, a positron emitter, may prove to be superior to ^{201}Tl, sestamibi, and tetrofosmin. These images, however, require a dedicated PET scanner, which increases the cost and has had limited application to date.

Positive imaging with nonspecific isotopic agents may identify tumors that could be amenable to surgical treatment or external beam radiotherapy as well as lung metastatic lesions that might concentrate ^{131}I when a therapeutic dose is given (67). In patients with an increased serum Tg level and negative ^{131}I WBS, some authorities have administered a large therapeutic dose of ^{131}I without

any additional imaging procedures—a decision based on the Tg level alone (68). An alternative approach is to perform a turnover study with ^{131}I. Serial 24-hour urine collections and whole counts are used to demonstrate whether ^{131}I is being organified by thyroid tumor metastatic lesions and, therefore, can be used as therapy (69).

Periodic surveillance with radioiodine WBS is performed by many endocrinologists in some patients with FCDC even without evidence of recurrent or persistent disease. These include high-risk patients with no abnormalities evident on physical examinations, low serum Tg levels, and normal findings on conventional imaging studies and some low-risk patients, particularly those within several years of diagnosis or RRA or those with positive TgAb. In many TgAb-negative patients, the combination of ^{131}I imaging with rhTSH and determination of rhTSH-stimulated Tg levels is emerging as an alternative to standard thyroid hormone withdrawal WBS (42).

In patients with MTC, several isotopic scanning agents are useful for identifying residual or recurrent tumor. ^{111}In pentetreotide, a somatostatin analogue, is currently the isotopic scan of choice in the United States. Other agents include radioiodinated metaiodobenzylguanidine and labeled anti-carcinoembryonic antigen (CEA) antibodies (70). Ultrasonography, MRI, and CT scanning of the neck and mediastinum may be helpful in the calcitonin-positive and clinically tumor-negative patient, as are PET scanning, bone scanning, and CT scanning of the liver (Table 3) (71,72).

PERSISTENT OR RECURRENT DISEASE

Secondary Surgical Intervention

When FCDC recurs locally, surgical excision is usually the therapy of choice. This treatment includes resection of lymph nodes and local tissue recurrences and, rarely, tracheal and esophageal resection. Bulky mediastinal lesions should be considered for surgical intervention if ^{131}I is ineffective. Metastatic lesions to the lungs are generally multifocal. Occasionally, however, surgical resection is indicated in patients with FCDC for a focal pulmonary or rib metastatic lesion or for a single pulmonary metastatic tumor that has demonstrated rapid growth in the face of other stable pulmonary metastatic disease. In long bones, lesions due to FCDC are sometimes excised by orthopedic surgeons, especially when they are bulky or when a risk of pathologic fracture exists. When lesions threaten the spinal cord, neurosurgical resection with or without prior focal embolization should be considered, with or without spinal fusion. In selected cases, isolated cerebral lesions metastatic from FCDC may necessitate resection.

Radioactive Iodine

Radioiodine therapy (^{131}I) is generally administered for FCDC when metastatic disease is discovered by radioiodine scanning (73,74). Of the three dosimetric methods available, the simplest and most widely used is the administration of a large fixed dose of ^{131}I. Typically, patients with nodal metastatic lesions that are not large enough to excise are treated with 100 to 175 mCi (3,700 to 6,475 MBq) of ^{131}I. Locally recurrent, invasive FCDC is usually treated with 150 to 200 mCi (5,550 to 7,400 MBq) of RAI after surgical resection or when a surgical procedure cannot be performed. Patients with distant metastatic involvement are usually treated with 200 mCi (7,400 MBq) of ^{131}I. Diffuse lung metastatic growths that concentrate more than 50% of the diagnostic dose of ^{131}I may be treated with a reduced dose of ^{131}I to avoid lung injury. A retained dose to the lungs of up to 80 mCi is generally thought to avoid radiation-induced pneumonitis or fibrosis. Doses in the range of 100 to 200 mCi (3,700 to 7,400 MBq) of ^{131}I may cause nausea and vomiting, salivary gland damage characterized by acute and recurrent parotid swelling, and decreased production of saliva. Doses of RAI as high as 300 mCi (11,100 MBq) are occasionally given to older patients whose advancing distant metastatic lesions demonstrate minimal radioiodine uptake.

A second approach uses quantitative dosimetry methods to calculate the administered dose of ^{131}I on the basis of estimated tumor uptakes. Calculated doses of 30,000 rad are sufficient to ablate residual thyroid tissue (75). Nodal metastatic lesions are unlikely to respond if the administered dose is <3,000 to 4,000 rad, with a goal of 10,000 ± 2,000 rad (76). For metastatic lesions that will receive only a few hundred rads, doses from 150 to 200 mCi (5,550 to 7,400 MBq) of ^{131}I should be considered in the setting of surgical excision or external irradiation. When resection or external irradiation is not possible (for example, in patients with multiple pulmonary lesions), however, high-dose radioiodine therapy is administered. Although serum Tg levels may decline in these cases, the ultimate effect on tumor control is unknown.

Some medical centers calculate the maximal "safe" dose of radioiodine, defined as that dose that delivers a maximum of 200 rad (2 Gy) to the blood, whole-body retention at less than 120 mCi (4,440 MBq) at 48 hours, and the amount in the lungs at less than 80 mCi (2,960 MBq) when pulmonary uptake is diffuse. Some centers use this approach only when the radiation dosage to metastatic lesions cannot be calculated. Others use this approach for all cases in which radioiodine is administered (77).

Very high cumulative doses (1,000 mCi) of ^{131}I have been associated with a small but significant increase in bladder cancer and breast cancer. Acute myelogenous leukemia has been reported in 5 of 1,000 patients treated with large doses of ^{131}I, greater than expected for the general population. This occurrence is very unlikely if the total blood dose is less than 2 Gy per administration (74). Bone marrow depression, usually transient, including anemia, leukopenia, and thrombocytopenia, occurred in patients treated with very large doses of ^{131}I but has been reported not to occur with use of modern dosimetry.

Before treatment with ^{131}I, a 10- to 30-day low-iodine diet may enhance the uptake of the isotope by iodine-concentrating cells. If the patient has normal renal function and good hydration, uptake usually occurs within 3 days.

Table 3
Imaging Modalities Used in Follicular Cell-Derived Cancers*

Imaging study	Principal use	Comment
Chest radiography	Assessment of increasing Tg level	Little utility with low Tg levels (56)
Neck ultrasonography	Surveillance for cervical nodes or local recurrence	Operator dependent
Neck CT or MRI	Establishing tracheal invasion; evaluating posterior neck area	Not as sensitive as ultrasonography in expert hands
Chest helical or spiral CT or chest MRI	Surveillance for pulmonary metastatic lesions in high-risk patients; evaluation of mediastinum; better for calcification than MRI	Far superior to chest radiography for micronodular disease
MRI	Defining neck anatomy; distinguishing tumor from fibrosis; identifying muscle invasion	Alternative to neck CT; images in 3 planes
Bone scan	Documenting bone metastatic lesions; clarifying bone pain	Poor screen (most FCDC metastatic lesions are lytic) (71)
^{131}I body scan	Detecting disease and determining whether it can be treated with ^{131}I	At most, 75% of untreated lesions are detected
Thallium body scan	WBS negative, Tg level high	Least effective nonspecific method
Sestamibi body scan	WBS negative, Tg level high	Poor mediastinal imaging (myocardial uptake); strap muscles light up; image quality appears time dependent
Tetrofosmin body scan	WBS negative, Tg level high	Least experience of gamma emitters; mixed preliminary reports
Fluorodeoxyglucose PET scan	WBS negative, Tg level high	Probably best nonspecific imaging modality; detects metabolically active, poorly differentiated disease; expensive; not widely available; not good for brain because of intense brain uptake
Posttreatment scan	Most sensitive ^{131}I imaging study (“stunning” notwithstanding) (72)	Generally recommended
^{123}I body scan	Alternative to ^{131}I pretreatment scan	Avoids stunning; currently being investigated
^{131}I turnover study	May be used to decide on ^{131}I therapy and calculate permissible doses when WBS negative and metastatic disease present. In presence of detectable disease, may be used to calculate maximal allowable dose to whole body or pulmonary metastatic lesions (or both)	Labor intensive; not widely used

*CT = computed tomography; FCDC = follicular cell-derived cancer; MRI = magnetic resonance imaging; PET = positron emission tomographic; Tg = thyroglobulin; WBS = whole-body scanning.

During this time, increased oral intake of fluids will augment urine output and minimize bladder injury from dehydration.

In addition, a practical suggestion is that the patient should suck on a lemon drop to stimulate salivary flow and avoid sialadenitis. Therapeutic doses of ^{131}I may reduce the sperm count for several months, and most authorities recommend that women avoid pregnancy for at least 6 months. Lastly, constipation should be treated with cathartics to reduce gonadal and colonic irradiation.

Posttreatment WBS should be done 4 to 10 days after RAI therapy to document the extent of ^{131}I uptake by the FCDC. About 10% of such scans show lesions not detected on the diagnostic scan done before therapy. Posttreatment scans are most likely to reveal clinically important new information in patients younger than 45 years who have received RAI therapy in the past. They are also likely to yield the most information when diagnostic scans have been noncontributory ("negative") and serum Tg concentrations are very high. In this situation, 10 to 50% of high-risk patients with high Tg levels and negative diagnostic WBS may prove to have metastatic tumors in the lungs or bones. Considerable controversy prevails about the use of ^{131}I therapy in the patients with negative scans and high serum Tg levels (67,68).

External Irradiation

External irradiation is rarely used as adjunctive therapy in the initial management of patients with FCDC (78,79). It may be beneficial, however, in patients with poorly differentiated (higher histologic grade) tumors that do not concentrate RAI. It also may be considered in the postoperative management of patients with FCDC who have gross evidence of local invasion and who are presumed to have microscopic residual disease after primary surgical treatment. A similar argument can be made for patients with MTC who have locally invasive disease. No convincing efficacy has been found, however, in irradiating the neck and mantle of patients with MTC who have postoperative hypercalcitoninemia but no imaging or clinical evidence of persistent disease.

The situation differs considerably with respect to less well-differentiated thyroid malignant lesions. Radiation therapy is almost routinely performed after biopsy or subtotal tumor resection for anaplastic thyroid cancers. Similarly, it is routinely used to treat the thyroid and mantle, after accurate disease staging, in patients with primary lymphoma of the thyroid. External irradiation is also useful for localized bony metastatic lesions, particularly those associated with pain.

MEDULLARY THYROID CARCINOMA

Medullary carcinoma constitutes 6 to 8% of thyroid cancers, of which approximately 75% are sporadic and 25% are hereditary. MTC represents a malignant transformation of neuroectodermally derived parafollicular C cells. Therefore, its behavior and management differ from these features described for well-differentiated follicular-derived thyroid carcinomas (80).

Sporadic Medullary Carcinoma

Fewer than 1 in 200 clinically apparent solitary thyroid nodules may harbor a medullary carcinoma (81). The diagnosis of sporadic medullary carcinoma may be suspected on the basis of characteristic cytologic features on FNA and immunostaining for calcitonin and confirmed by a high preoperative serum calcitonin level. Because these features often are not sought or recognized at the time of FNA, the diagnosis is usually first made at the time of surgical removal of a thyroid nodule. Although studies (82-85) have suggested that, in the evaluation of a thyroid nodule, the routine measurement of serum calcitonin is a cost-effective and important technique to avoid missing this potentially lethal tumor, not all clinicians agree that screening calcitonin is useful (4,81). Calcitonin should be measured in the setting of a thyroid biopsy specimen with atypical features or an apparently anaplastic or poorly differentiated tumor in a young person. Suggestive cytologic features should prompt a request for calcitonin immunostaining of the biopsy specimen. Ultrasonography may reveal bright echogenic foci (corresponding to calcium). Abnormal lymph nodes may be seen as well (86), prompting a calcitonin measurement preoperatively.

If medullary carcinoma is suspected preoperatively, the extent of the disease may be evaluated by ultrasonography, CT, or MRI of the neck and CT of the chest and abdomen. The preoperative calcitonin level correlates well with tumor bulk, nodal and distant metastatic involvement, and postoperative calcitonin normalization (87,88). In the absence of a family history of MTC, usually no clues distinguish MTC from other thyroid nodules. Chronic diarrhea, lichen amyloidosis, or features suggestive of ectopic ACTH (adrenocorticotropic hormone) syndrome are rarely present. When MTC is diagnosed or suspected, preoperative screening for pheochromocytoma is imperative.

Surgical treatment of MTC should include total thyroidectomy, central compartment lymph node dissection, and ipsilateral (unilateral) modified radical neck dissection (89). The tumor is staged in accordance with the AJCC system (see discussion of staging systems earlier in these guidelines), in which data are recorded about tumor size, lymph node involvement, and distant metastatic lesions. Risk factors for recurrence and death include tumor size, preoperative calcitonin level, advanced age, extrathyroid tumor extension, progression of cervical nodal disease to the mediastinum, extranodal tumor extension, and incomplete tumor excision.

Serum calcitonin levels should be measured 8 to 12 weeks postoperatively to assess the presence of residual disease. If preoperative staging had not been performed, residual postoperative calcitonin should prompt a search for locally resectable disease in the neck as well as metastatic disease in the bones, lungs, or liver. For residual local disease, ultrasonography of the neck is the most

sensitive and cost-effective procedure. The search for metastatic disease may include CT and MRI scans, scanning with sestamibi, radioiodinated metaiodobenzylguanidine, octreotide (indium pentetreotide), and ^{131}I anti-CEA antibody. ^{99m}Tc methylene diphosphonate, ^{99m}Tc dimercaptosuccinic acid, and ^{201}Tl have also been used with variable success (90-92). Unfortunately, localization of residual disease is often difficult or impossible when the calcitonin level is less than 1,000 pg/mL—an indication of a relatively small residual tumor burden. Additional methods of localizing residual disease include selective venous sampling of the neck and viscera for calcitonin and laparoscopic liver biopsy. Identifying distant disease may be important for obviating extensive neck dissection in a curative attempt (89).

The behavior of residual disease may vary from indolent to aggressive (93). Tumor pathologic features, such as absent amyloid staining, low density of calcitonin staining, or aneuploidy, and production of other neuroendocrine products may correlate with a worse prognosis but are of uncertain use in planning subsequent clinical management (80). In hereditary disease (see next section), the type of syndrome has prognostic significance. Physicians have variously advocated either aggressive surgical removal of residual cervical and mediastinal disease or conservative management. Adjuvant therapy, including external beam radiotherapy and chemotherapy, is of unproven benefit but is often used when the patient has a potential risk of either obstructive symptoms or relentless cancer growth. Experimental therapy with high-dose ^{131}I anti-CEA antibody is currently under investigation. Most authorities advocate careful observation and conservative management, even in the face of known metastatic disease, because of the relative lack of efficacy of currently available adjuvant therapy.

Pathologically, the presence of bilateral thyroid disease, including staining for C-cell hyperplasia, should be sought as a possible reflection of a newly diagnosed hereditary form of the disease. Because somatic mutations of the *RET* proto-oncogene are frequently present in sporadic disease, genetic analysis of the tumor is not warranted. Search for a germline mutation, however, is the most cost-effective means of identifying new families at risk (94). In one series of 101 apparently sporadic cases so tested, 4 new families were detected and 2 de novo mutations were found, whereas in another series, 5 of 21 cases (24%) represented new kindreds (95).

Hereditary Medullary Carcinoma

Hereditary MTC occurs as part of three familial syndromes: MEN type IIA, MEN type IIB, and isolated familial MTC. MEN type IIA is most common, representing two-thirds of the hereditary cases. The syndrome includes MTC (generally bilateral), pheochromocytoma or adrenal medullary hyperplasia (also bilateral), and hyperparathyroidism (which often involves all four parathyroid glands). Although MTC is expressed in 100% of patients, pheochromocytoma and hyperparathyroidism are not (in 50% and 35%, respectively). MEN type IIB includes MTC, pheochromocytoma, marfanoid habitus, mucosal neuromas involving the lips, tongue, eyes, and pharynx, and ganglioneuromatosis of the gastrointestinal tract. MTC in MEN type IIB is more virulent and manifests at an earlier age. Familial MTC is defined by the presence of four or more cases in a family without other associated endocrinopathy (80). Its behavior is generally more indolent than either MEN type IIA or IIB.

The diagnosis and management of these disorders have been revolutionized by the finding of specific germline mutations of the *RET* proto-oncogene, which codes for a tyrosine kinase receptor, expressed in derivatives of neural crest tissues. Families with MEN type IIA have missense mutations in one of five cysteine codons in exon 10 (609, 611, 618, and 620) and exon 11 (634) located in the extracellular cysteine-rich domain adjacent to the membrane. These mutations are present in more than 95% of families with MEN type IIA and 85% of families with familial MTC. Ninety-five percent of MEN type IIB families have a single point mutation at codon 918 (exon 16), with a methionine for threonine substitution. This codon lies in the region that encodes the pocket that recognizes the substrate of the tyrosine kinase receptor. In families with familial MTC, two additional mutations in the intracellular tyrosine kinase domain have been found at codon 768 (exon 13) and 804 (exon 14). DNA analysis by polymerase chain reaction yields 100% sensitivity and specificity in families with a known mutation. Some correlation exists between genotype and phenotype, with the codon 634 mutation having a higher frequency of pheochromocytoma and hyperparathyroidism than other mutations, and cys→arg mutations at this site causing an even greater frequency of hyperparathyroidism (96). No relationship has been found between genotype and disease virulence within the MEN type IIA and familial MTC families. Genetic testing should begin by no later than age 6 years in MEN type IIA and shortly after birth in MEN type IIB families (because of the earlier onset and greater virulence of the latter) (97).

The current standard of care is to recommend surgical treatment for MTC family members diagnosed with appropriate *RET* mutations. This treatment may be accomplished as early as age 2 years, if appropriate surgical facilities are available. Preoperatively, all subjects should undergo confirmatory analysis of a germline *RET* mutation, and all should be screened for pheochromocytoma. Baseline serum calcitonin should be measured. An ultrasound study of the neck may be useful. Previously, the response to pentagastrin was also measured as a guide to tumor bulk. Currently, synthetic pentagastrin is unavailable, and the use of intravenous calcium stimulation would add little to preoperative management.

In the rare situation of a clearly affected kindred with a currently unrecognizable *RET* mutation by direct DNA analysis, linkage analysis may be performed if DNA is

available from at least two affected family members. The results may have an error rate of 2 to 5%, attributable to recombination (98). When this method is unsuccessful, baseline serum calcitonin or periodic calcitonin stimulation studies (for example, pentagastrin when available or calcium) (99) are necessary to screen for affected individuals. Although 95% of patients with MEN type IIA are diagnosable by age 35 years, similar data are unavailable for familial MTC. False-positive and false-negative results have been reported for provocative biochemical tests (pentagastrin or calcium infusion).

Affected subjects should undergo prophylactic total thyroidectomy and central compartment lymph node dissection (100). In one report, 3.4% of patients who underwent operative treatment for the presence of *RET* mutation had histologically normal glands (101), whereas 8.4% had cervical node metastatic lesions, even with a primary tumor smaller than 1 cm. Current recommendations include prophylactic central neck node dissection independent of tumor size, particularly in patients with a focal ultrasound abnormality, high levels of serum calcitonin, and age more than 10 years. Some surgeons recommend bilateral modified radical neck dissection in this circumstance (89). No consensus exists about parathyroid gland management in patients with MEN type IIA. Some surgeons recommend prophylactic total parathyroidectomy in conjunction with autotransplantation of parathyroid tissue, in anticipation of additional operations that may compromise parathyroid function or possible future hyperparathyroidism. Most surgeons, however, try to preserve parathyroid function as in any bilateral thyroidectomy, and they may use localizing clips or long permanent sutures to assist in identification of the parathyroid glands should reoperation become necessary. Postoperative follow-up is dictated by the stage of disease at the time of initial surgical intervention and the projected risk of recurrence. Periodic surveillance for pheochromocytoma should be continued indefinitely for patients with familial MTC.

ANAPLASTIC THYROID CARCINOMA

Anaplastic or undifferentiated thyroid carcinoma is a highly aggressive tumor. The tumor is uncommon, fewer than 300 cases occurring each year in the United States. Approximately 1.6% of all thyroid cancers are anaplastic (1). Anaplastic thyroid carcinoma is primarily a tumor in older age-groups, most commonly in the fifth to sixth decades of life, but can be found in younger patients in rare instances. In several studies. In several studies, patients younger than the age of 50 years constitute from 4 to 10% of patients with anaplastic carcinoma (102,103)

Anaplastic thyroid carcinoma most commonly manifests as a rapidly expanding thyroid mass. Associated symptoms include hoarseness, dyspnea, dysphagia, and cervical pain. Other manifestations include superior vena cava syndrome, ball-valve tracheal obstruction, hyperthyroidism due to necrosis of normal thyroid tissue and release of thyroid hormone (104), and symptoms indicative of metastatic involvement of the lung, bone, brain, and, rarely, skin and bowel (105,106). The duration of symptoms is generally short, ranging from a few weeks to a few months. At diagnosis, the primary tumor is larger than 5 cm in 80% of patients, and it may be multiple and bilateral (107). Extension of the mass outside the thyroid gland, cervical node metastatic lesions, vocal cord palsy, or some combination of these findings occurs in 50% of patients (104).

FNA biopsy is the diagnostic procedure of choice for evaluation of anaplastic thyroid carcinoma manifesting as an enlarging thyroid mass or cervical node enlargement. Radionuclide scanning is generally unnecessary, although the tumors are “cold” on radioiodine scans (104-106). Pathologically, anaplastic thyroid carcinoma is grossly tan-white, fleshy, and large; areas of necrosis and hemorrhage are evident. Histologically, three general and predominant patterns are seen (often coexisting): spindle cell, giant cell, and squamoid cell. Common features are large foci of necrosis, invasiveness, and predilection for growth into vascular structures. Cytologically, the tumor is characterized by high mitotic activity and atypical appearing cells (104,108).

Treatment of anaplastic thyroid carcinoma is controversial. Surgical biopsy may be necessary for confirmation of the diagnosis and protection of the airway (106,108), although some surgeons attempt primary resection. The value of prophylactic tracheostomy for survival or palliation is uncertain. Patients with a tracheostomy could be subject to local wound healing complications that could prevent or delay the use of other modalities, such as postoperative external beam radiotherapy (105,106,109).

External beam radiotherapy can aid in local disease control, although anaplastic thyroid carcinoma is generally considered a radioresistant tumor in comparison with other solid neoplasms. Several studies have indicated improvement in overall survival and resectability with the use of external beam radiotherapy preoperatively and in combination with chemotherapy (110,111).

Chemotherapy may prolong survival is some patients but generally is not successful in altering the uniformly fatal outcome of this tumor. Chemotherapeutic regimens including doxorubicin have been used most frequently (110). Other commonly used agents have included cisplatin, bleomycin, vincristine, and 5-fluorouracil in various combinations (112). The use of newer agents for treatment of anaplastic thyroid carcinoma is currently under investigation (106).

Local tumor control seems the most practical management of this aggressive neoplastic process, although each patient may require a different and individualized approach. The use of combination therapies to include preoperative irradiation and chemotherapy followed by aggressive local tumor resection may yield an increased duration of survival. Because of the high rate of metastatic disease found at diagnosis, however, provision of appropriate palliative measures and support may be more important.

CHEMOTHERAPY

Chemotherapy for patients with differentiated FCDC is used for symptomatic or advancing tumors that are surgically unresectable, are unresponsive to RAI, and have been treated with, or are not amenable to, external irradiation (31,113). Nevertheless, no chemotherapeutic regimen has been consistently successful, although both combination chemotherapy and doxorubicin monotherapy have been used. In contrast, in disseminated thyroid lymphoma, the treatment of choice after initial surgical intervention should routinely include an anthracycline-based chemotherapy, usually a "CHOP" regimen—cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin (vincristine), and prednisone. The survival of patients with anaplastic thyroid cancer, however, has not been altered by surgical treatment, radiation therapy, or chemotherapy alone. The most effective single drug against anaplastic thyroid cancer has been doxorubicin, although a few responses have been reported with combined doxorubicin and cisplatin therapy. Unfortunately, in patients with anaplastic cancer, only combined multimodality therapy has improved the rate of local tumor control and thereby avoided death from suffocation.

CONCLUSION

These AACE/AAES guidelines represent a consensus management approach to patients with thyroid carcinoma. The field is highly complex, and a considerable diversity of opinion prevails. The spectrum of that diversity of opinion is represented by the Thyroid Carcinoma Task Force that developed these guidelines. Important goals of this document are to highlight the role of the clinical endocrinologist in coordinating the comprehensive care of the patient with thyroid cancer and to emphasize the cost-effective provision of high-quality care. Adherence to these guidelines should eliminate the possibility of either overaggressive treatment in a patient with an excellent prognosis or inadequate therapy for the unusual patient with a high risk of tumor recurrence and possible death from cancer.

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