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Thyroid Cancer: 1999 Update

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Evaluation of Solitary Thyroid Nodules

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Thyroid nodules are common; it is estimated that approximately 4% to 7% of the adult American population has a palpable thyroid nodule, and autopsy and high-resolution ultrasonography studies suggest that up to 50% of adults may have nodules within their thyroid gland.[1,2] In contrast, malignant thyroid nodules are relatively rare; with approximately 17,200 new cases of thyroid cancer reported each year, malignant thyroid nodules represent only 1% of all malignancies and 0.5% of all cancer-related deaths.[3,4] Because the overwhelming majority of thyroid nodules are benign, the clinician is faced with the difficult task of trying to identify the small number of patients with malignant nodules, which require surgical treatment, among the large number of patients with benign thyroid nodules. The clinical evaluation of a solitary thyroid nodule initially involves identifying risk factors that may increase the probability that a given nodule is malignant. These characteristics include prior neck irradiation; family history; age; whether or not the nodule is solitary; characteristics of the nodule, including size, consistency, and/or fixation; whether there are any enlarged lymph nodes; hoarseness; and pressure symptoms. Although thyroid function tests are often done, it is unusual for thyroid cancer to cause significant alterations in thyroid function.

Other modalities that have been used in differentiating benign nodules from malignant ones include thyroid suppression therapy, cervical ultrasonography, and thyroid scintigraphy. First, thyroid suppression therapy, although frequently used, has not been shown to cause a statistically significant decrease in the size of nodules when compared with placebos in recent studies.[5,6] There are also numerous reports of nodules that decreased in size during suppression therapy but subsequently turned out to be malignant.[7] Second, cervical ultrasonography can identify extremely small nodules in the range of 1 mm in diameter; however, there are no ultrasonographic criteria that are pathognomonic for malignancy.[8] Third, thyroid scintigraphy has been used enthusiastically in the past to differentiate between benign and malignant nodules. If one looks at the scintigraphic characteristics of all nodules, 84.0% are cold (nonfunctioning), 10.5% are warm (having uniform tracer uptake), and 4.0% are hot (hyperfunctioning).[9,10] Cancer is present in approximately 16% of cold nodules, 9% of warm nodules, and 4% of hot nodules. Therefore, if a nodule is cold, there is an 87% sensitivity for cancer, but specificity is only 30%.

Over the past 10–15 years, fine-needle aspiration (FNA) biopsy has emerged as the most accurate and cost-efficient way to differentiate benign from malignant nodules with an accuracy rate approaching 95%.[11] FNA

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biopsies are performed with 21 to 25 gauge needles, making three to five aspirations of the nodule. The smears are then alcohol-fixed and air-dried. Papanicolaou's and Giemsa (Diff-Quik) stains are performed, and smears containing 6–8 medium-sized fragments of follicular epithelium on at least two slides are defined as adequate. Using this FNA technique has decreased surgical intervention by 25% while increasing the identification of cancer in surgically excised specimens from 15% to over 30%.[12]

Cytological results from FNA biopsies are usually reported in one of four categories: (1) positive for malignancy (papillary or medullary carcinoma), (2) indeterminate for malignancy (follicular neoplasm), (3) negative for malignancy (colloid nodule), and (4) inadequate specimen (insufficient tissue for interpretation). Large studies have demonstrated that the false-positive rate for FNA biopsy is close to 0% and the false-negative rate is 0% to 2%.[13,14] FNA biopsy is safe, reliable, and accurate, yet approximately 15% to 20% of FNA biopsy results are interpreted as indeterminate, and 5% to 10% of biopsy specimens are judged to be inadequate.

Controversy surrounding FNA biopsy involves indeterminate cytologies, because 10% to 30% of nodules reported as indeterminate will turn out to be malignant after thyroidectomy.[15] Most cytopathologists will further subcategorize the group of indeterminate cytologies as shown in Table 1.[15] Cytologies that are suspicious for papillary carcinoma are classified as such because they do not satisfy the criteria for the cytological diagnosis of papillary carcinoma of the thyroid outlined by Kini.[16] Between 60% and 90% of indeterminate FNA biopsy specimens described as suspicious for papillary carcinoma will turn out to be malignant.[15,17] Therefore, this cytological result should prompt thyroid lobectomy (see algorithm in Fig. 1). If the surgeon is a proponent of total or near-total thyroidectomy for well-differentiated thyroid cancer, then a frozen-section analysis of the lobectomy specimen should be performed; if the nodule is malignant, then the total thyroidectomy is completed. In contrast, indeterminate FNA cytologies that are interpreted as hypercellular follicular aspirates with colloid

TABLE 1. *Subclassification of indeterminate FNA cytologies*

Indeterminate Cytology	Percent indeterminate FNA biopsies	Percent malignant
Suspicious for papillary carcinoma	10	90
Follicular neoplasm	55	20
Hurthle cell neoplasm	20	30
Hypercellular follicular aspirates	15	0

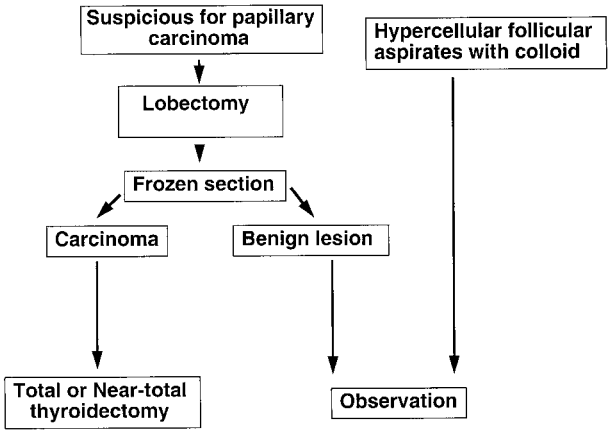

FIG. 1. Management algorithm for indeterminate FNA cytology.

are almost always benign; in these cases, observation with or without thyroid suppression is adequate treatment.[15]

Indeterminate lesions interpreted as follicular or Hurthle cell neoplasms can only be deemed malignant if histological evidence of capsular, lymphatic, or vascular invasion is identified. These histological findings require more tissue than can be obtained by FNA biopsy; a cytopathologist cannot differentiate between follicular or Hurthle cell adenoma and carcinoma based solely on a cytological examination.[18–20] Use of additional cytological parameters, such as the cellular pattern,[21–23] nuclear diameter,[24] number and margination of nucleoli,[25,26] and DNA pattern as measured by flow cytometry,[27–29] has met with limited success in differentiating follicular or Hurthle cell carcinomas from adenomas. A repeat FNA biopsy may eliminate the misdiagnosis of benign lesions, although it cannot differentiate between benign and malignant follicular lesions.[30,31] In addition, the use of thy-

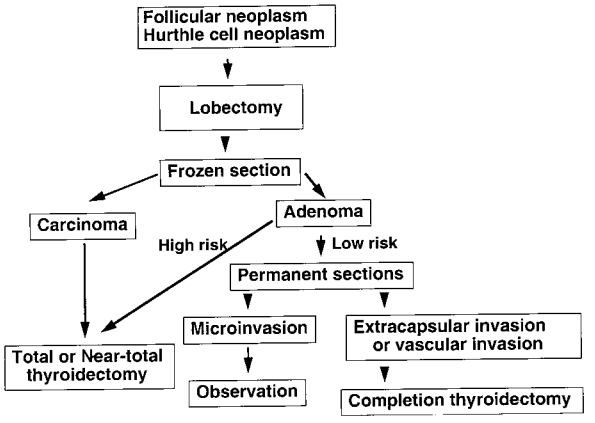

FIG. 2. Management algorithm for indeterminate FNA cytology. Thyroid scintigraphy is performed in patients with suppressed TSH levels that suggests a functioning (hot) nodule.

roid suppression in conjunction with a repeat FNA biopsy has been proposed as a means of observing and treating individuals with indeterminate FNA biopsy results.[32] Although levothyroxine therapy is commonly used, recent studies have demonstrated that thyroid-stimulating hormone (TSH) suppression will not shrink or alter the histological appearance of follicular lesions.[6]

At the current time, the most useful approach for the treatment of indeterminate follicular and Hurthle cell lesions involves assessing the likelihood of malignancy by examining various clinical parameters. Several studies have demonstrated an improved, but not perfect, ability to predict malignant potential using the size of the lesion and age of the patient.[15,33] Indeterminate follicular or Hurthle cell neoplasms in patients over 50 years of age with nodules >4 cm in diameter have a 40% to 60% incidence of being malignant compared with an incidence of 10% in individuals with smaller nodules (<4 cm), or under the age of 50. Patients with follicular neoplasms and a suppressed TSH can be screened using thyroid scintigraphy. If the patient's scan shows a hot nodule (uncommon in the absence of suppressed TSH), malignancy is very rare.

Although controversial, we perform, at the time of thyroid lobectomy, an intraoperative frozen-section evaluation of the nodule to confirm the suspected pathology[15,34,35] (Fig. 2). If evidence of capsular or vascular invasion (carcinoma) is identified, a total or near-total thyroidectomy is performed (the controversy regarding a unilateral versus bilateral operation for well-differentiated thyroid cancer will be addressed later in this report). If no evidence of carcinoma can be identified, a bilateral operation is performed only in patients deemed to be in the high-risk category on the basis of age (>50 years old) and nodule size (>4 cm). For low-risk patients, one should wait for permanent-section evaluation to be completed and the operation is terminated. In young patients whose final pathology demonstrates only minimal capsular invasion without vascular invasion, observation after thyroid lobectomy is reasonable due to their excellent prognosis on the basis of the AMES (age, metastases, extrathyroidal extension, size) and AGES (age, grade, extrathyroid extent, size) criteria.[36,37] If the final pathology demonstrates extension beyond the thyroid capsule or vascular invasion, a completion total thyroidectomy is performed.

Differentiated Thyroid Cancer: Less Than Total Thyroidectomy

Ashok R. Shaha, MD

The management of thyroid cancer continues to be a subject of major controversy. Issues related to diagnostic evaluation and the extent of thyroidectomy have generated considerable debate. Determining the proper extent of thyroid resection—routine total thyroidectomy or less-than-total thyroidectomy—has generated considerable literature and stimulated many panel discussions at various national meetings. It has also polarized two groups of physicians with strongly held beliefs. Unfortunately, most of the reports in the literature are retrospective and are therefore difficult to interpret. A prospective randomized study of total thyroidectomy versus thyroid lobectomy in patients with well-differentiated thyroid cancer is almost impossible to complete because of the excellent outcome of the disease (long survival duration), the required long-term follow-up, and the large number of patients needed to show any meaningful statistical differences in outcome.

The question most frequently posed is, "What is the best operation for a patient who presents with a solitary thyroid nodule?" Obviously, if there is gross disease in both lobes of the thyroid, total thyroidectomy is the most appropriate surgical procedure. However, in a young individual with a primary carcinoma <4 cm in diameter, the controversy continues regarding whether a routine total thyroidectomy is necessary or a less-than-total thyroidectomy is sufficient. The major arguments for a total thyroidectomy include the presence of microscopic disease in the opposite lobe, the need for adjuvant radioiodine therapy, the ability to use thyroglobulin as a postoperative tumor marker (it can be used only after total thyroidectomy), and the hypothetical (small) risk of anaplastic transformation. Based on these arguments, authors have advocated the routine use of total thyroidectomy for well-differentiated thyroid cancer.[38,39] In contrast, the treatment of lymph node metastases is well defined: if clinically obvious, nodal metastases are treated surgically with neck dissection. If clinically palpable nodes are present in the lateral neck, a modified neck dissection should be performed, preserving the sternocleidomastoid muscle, accessory nerve, and jugular vein.

Our understanding of well-differentiated thyroid cancer has improved considerably in the past two decades with identification of prognostic factors and analysis of risk groups.[36,37,40–46] Reports from the Mayo Clinic and Lahey Clinic analyzed various clinical and pathological factors in patients with well-differentiated thyroid cancer and defined poor prognostic factors including advanced age, high tumor grade, the presence of distant metastasis, increased tumor size, and the presence of extrathyroidal tumor extension. Based on these prognostic factors, they divided their patients into low- and high-risk groups. The mortality rate in the low-risk group was $<2\%$, whereas in the high-risk group, mortality was 46%.[36,37,39,40] Researchers at Memorial Sloan-Kettering Cancer Center (MSKCC) described similar prognostic factors, which included tumor grade, age, tumor size, and the presence of distant metastasis or extrathyroidal tumor extension. The MSKCC authors divided their patients into low-, intermediate-, and high-risk groups. The long-term (20 years) survival rate in these three risk groups was 99%, 85%, and 57% respectively (Table 2).[41,45]

The above information is extremely helpful in understanding the biology of thyroid cancer and making appropriate decisions regarding the need for total versus less-than-total thyroidectomy. Obviously, a nodulectomy or partial thyroidectomy should not be performed because of the high risk of local recurrence and the inability to achieve adequate margins of resection. If a patient belongs to the high-risk group, consideration should be given to total thyroidectomy at the time of initial surgery because the patient may need radioiodine therapy in the future. It is generally believed that 80% of patients will do well with lobectomy alone; 5% of patients will do poorly regardless of the surgical procedure performed because of the aggressive nature of thyroid cancer in selected patients; and 15% of the patients will need total thyroidectomy and adjuvant radioiodine or external-beam radiotherapy to control locally advanced disease. In patients with papillary thyroid cancer, the clinical incidence of local recurrence in the contralateral lobe after unilateral lobectomy is generally $<5\%$, even though the incidence of microscopic multicentric disease

may be as high as 40% to 70%. The presence of such microscopic "laboratory cancer" has little prognostic significance.

The routine use of adjuvant radioiodine therapy is also controversial. When patients are divided into low- and high-risk groups, no specific indications exist for the routine use of radioiodine ablation in low-risk patients. This is because the outcome in these patients is excellent, and it is unlikely that radioiodine will have a major impact on long-term survival. Low-risk patients should receive thyroid suppression therapy (levothyroxine) and be observed. In the event of recurrence with distant metastasis, consideration should be given (at that time) to either completion thyroidectomy or radioiodine ablation of the other lobe. The argument in favor of total thyroidectomy based on ease of follow-up with thyroglobulin is also unfounded. Thyroglobulin is a nonspecific weak tumor marker, and the measurement of thyroglobulin levels during follow-up in low-risk patients with well-differentiated thyroid cancer remains investigational. Considering the above arguments, I believe that the minimal operation for a well-differentiated solitary thyroid cancer is lobectomy and isthmectomy; for the majority of patients, this is also the maximum operation required. In reviewing our large database of patients with papillary or follicular thyroid cancer (>1,000), there was no significant difference in outcome based on the operation performed in patients with thyroid cancers ≤3 cm in diameter.[42,45,46]

There are very few circumstances under which a surgeon should consider total thyroidectomy. These circumstances include a grossly abnormal contralateral lobe, a high-risk patient with either extrathyroidal tumor extension or a large primary tumor with major extracapsular tumor extension, massive lymph node metastases, or an elderly patient.[47,48] However, the routine use of total thyroidectomy in every patient who presents with a solitary thyroid nodule is not indicated.

One of the most common clinical problems involves a patient who is found to have a follicular adenoma on frozen-section analysis that is revealed to be follicular carcinoma on permanent-section analysis based on histological evidence of capsular invasion. These patients are often returned to the operating room for completion thyroidectomy. However, these patients generally fall into the low-risk group and have excellent long-term survival. If the patient's opposite lobe was normal at the time of initial surgery, the primary tumor should be reviewed to histologically assess the presence or absence of capsular and vascular invasion. If there is minimal capsular or vascular invasion, these patients generally have "nonthreatening malignancies," and no additional treatment is required unless there is major vascular invasion or other poor-risk prognostic factors.

Despite the information given above, there are very strong proponents of both total thyroidectomy and completion thyroidectomy. Such proponents are surgeons who are extremely well trained and have tremendous experience. There is absolutely no doubt that the complications of total thyroidectomy are minimal for well-trained, experienced thyroid surgeons. The incidence of one such complication, permanent hypoparathyroidism, is directly proportional to the extent of thyroidectomy and inversely proportional to the experience of the operating surgeon. However, we must recognize that the bulk of thyroid surgery is still performed by surgeons outside referral centers, where the incidence of complications may be higher than reported by experienced surgeons in major referral centers. The long-term complications of total thyroidectomy may be of greater concern to the patient than the disease itself. It is, therefore, very important to review prognostic factors and risk-group classification before the routine use of total thyroidectomy, and consideration should be given to the extent of thyroid resection appropriate for each patient.

Our practical approach to the operative management of solitary thyroid nodules includes an FNA biopsy and pathological assessment using frozen sections at the time of surgery. We carefully evaluate the opposite lobe for the presence of gross disease; if there are clinical abnormalities

TABLE 2. *Risk-group definitions in patients with well-differentiated thyroid cancer (MSKCC)*

Characteristic	Low	Intermediate	Intermediate	High
Age (years)	<45	<45	≥45	≥45
Distant metastasis	M0	M+	M0	M+
Tumor stage	T1, T2 (≤4 cm)	T3, T4 (>4 cm)	T1, T2 (≤4 cm)	T3, T4 (>4 cm)
Histology and grade	Papillary	Follicular and or high-grade	Papillary	Follicular and or high-grade
5-Year survival rate	100%	96%	96%	72%
20-Year survival rate	99%	85%	85%	57%

in the opposite lobe, a total thyroidectomy is performed. At the time of surgery, it is important to evaluate the tracheoesophageal, internal jugular, and superior mediastinal lymph nodes. If any of these nodes are enlarged, a central compartment dissection is done. Before the initial operation for a solitary thyroid nodule, the patient's risk-group classification should be assessed to determine the need for adjuvant radioiodine therapy. If the patient belongs to the high-risk group and radioiodine therapy is planned, it would be appropriate to consider total thyroidectomy, thereby avoiding the need for another operation. If the tumor is either adherent to or invading the tracheal wall, or if bulky metastatic disease is noted in either the contralateral neck or superior mediastinum, total thyroidectomy with appropriate clearance of lymph nodes is performed, followed by radioiodine therapy.

The survival of patients with well-differentiated thyroid cancer is generally decades long, making it difficult to develop clear recommendations for the extent of thyroid resection appropriate in all patients. A randomized prospective trial in low-risk patients will be virtually impossible because each patient is quite different, the treatment must be individualized, and the survival rate is so good that the study will not generate any meaningful statistical difference despite a long period of postoperative observation.

Differentiated Thyroid Cancer: Less Than Total Thyroidectomy

Robert A. Udelsman, MD, FACS

Few areas in endocrine surgery are more controversial than the management of well-differentiated thyroid cancer. Well-differentiated thyroid cancers are derived from the thyroid follicular cells and include papillary cancer (including mixed papillary-follicular carcinoma) as well as the follicular variant of papillary carcinoma. Follicular and Hurthle cell carcinoma are also considered to be well differentiated and, for the most part, are managed much like papillary carcinoma. Papillary thyroid carcinoma is the most common epithelial thyroid tumor, accounting for approximately 80% of all thyroid cancers. The major ongoing debate in the management of well-differentiated thyroid cancer is the proper extent of surgery at the time of initial thyroidectomy. Two schools of thought in this debate have emerged: one suggests that a total or near-total thyroidectomy is the ideal operation for the vast majority of patients with well-differentiated thyroid cancer, whereas the other suggests that patients can be stratified preoperatively according to identifiable risk factors to allow those who are at low risk (for both recurrence and death) to undergo a lesser procedure, usually in the form of a thyroid lobectomy. The arguments for total thyroidectomy are summarized in Table 3.

Mazzaferri and associates[7,49,50] have shown that for patients with tumors >1.5 cm in diameter, both recurrence and cancer-related mortality are reduced with near-total or total thyroidectomy in combination with adjuvant radioiodine ablation and long-term thyroid hormone suppression. The ability to perform radioiodine scans and/or therapy is dependent upon the residual amount of thyroid tissue left in situ. Therefore, if a thyroid lobe is left in situ, radioiodine therapy is, for the most part, impractical. In Mazzaferri's study,[49] successful ablation was achieved in 94% of patients who had <2 g of thyroid tissue compared with 68% of patients who had a large thyroid remnant. Radioiodine therapy itself has been shown to prolong survival and reduce recurrence rates in several studies.[49,51–53] These results have also been demonstrated in a series of nearly 1600 patients who were treated for well-differentiated thyroid cancer, at The University of Texas M. D. Anderson Cancer Center, in which radioiodine therapy was found to be the single most powerful prognostic indicator for increased disease-free survival.[53] Similar findings have been demonstrated by Mazzaferri as well as DeGroot and associates.[49,51]

TABLE 3. *Rationale for total thyroidectomy*

1. Improves ability to use postoperative radioiodine therapy.
2. Lowers dose of radioiodine needed for ablative therapy.
3. Allows monitoring of recurrence with radioiodine scans and serum thyroglobulin.
4. Improves survival in high-risk subsets of patients.
5. Decreases recurrence rates in all patients.
6. Reduces the risk of developing pulmonary metastases.
7. Can be performed with the same morbidity and mortality as that of a unilateral procedure.
8. Decreases the small risk of a differentiated cancer from becoming an undifferentiated cancer.

Total or near-total thyroidectomy may also allow for the administration of lower doses of radioiodine for successful ablation. In general, radioiodine doses in the range of 75–100 mCi are used for ablation. Smaller doses, usually 29.9 mCi, are now frequently used, making outpatient treatment possible for patients who have undergone total or near-total thyroidectomy. Additionally, low-dose ablative therapy was far more successful in patients who had total or near-total thyroidectomy compared with patients who had lesser procedures.[54]

Serum thyroglobulin has been shown to be the most sensitive marker for recurrent papillary carcinoma of the thyroid.[55] After ablating remnant thyroid tissue with radioiodine, serum thyroglobulin becomes a useful marker for recurrent disease. Furthermore, radioiodine scans can be used to diagnose and localize recurrent disease. This is important because the probability of persistent disease or death after treatment of recurrent thyroid cancer is less for patients with radioiodine-detected recurrent disease than for those with clinically diagnosed recurrence (9.5% vs. 54.0%).[56] With the use of recombinant thyroid-stimulating hormone (r-TSH) testing, which is likely to replace thyroid hormone withdrawal, patients will not have to experience the side effects of hypothyroidism associated with additional radioiodine scans.[57,58] It is likely that r-TSH will significantly change the manner in which patients with thyroid cancer are treated.

Total thyroidectomy is also associated with increased survival in subsets of patients.[49,51,59,60] Clark[61] reported

that total thyroidectomy reduced the thyroid cancer death rate from 5% to 2%. Also, DeGroot and Kaplan[62] found that total or near-total thyroidectomy in patients with papillary thyroid tumors >1 cm in size resulted in a decreased risk of death from cancer. Mazzaferri and colleagues[49,50] also reported improved mortality in patients with stage II or III disease who had a total or near-total thyroidectomy versus lesser procedures. Furthermore, researchers at the Mayo Clinic found that bilateral thyroid resection resulted in lower death rates in high-risk patients.[63] Therefore, the data overwhelmingly suggest that in high-risk patients, total or near-total thyroidectomy plus radioiodine therapy improves survival.

Similar studies have shown that total or near-total thyroidectomy reduces the recurrence rate in patients with papillary thyroid cancer.[7,50,51] These results have been demonstrated by McConahey and associates,[64] who demonstrated that the recurrence rate after thyroid lobectomy was 4 times higher than that after total or near-total thyroidectomy. Furthermore, DeGroot and Kaplan[62] reported that in all patients with papillary thyroid cancer, bilateral thyroid resection reduced the recurrence rate. Similar data have been shown in series from both Mazzaferri and the Mayo Clinic. Preventing recurrence is important because 50% of the patients who have a recurrence in the central neck ultimately die of thyroid cancer.[65] Furthermore, even low-risk patients, as defined by Cady and associates,[66] can develop recurrence after thyroid lobectomy; one-third of these patients will ultimately die of thyroid cancer. Additional data suggest that total thyroidectomy is associated with decreased risk of pulmonary metastases. Massin et al.[59] reported that of 831 patients with well-differentiated thyroid cancer, 58 (7%) developed subsequent pulmonary metastases. A clear stratification was noted in that the prevalence of pulmonary metastases was 1.3% in patients who had total thyroidectomy and radioiodine therapy, 5% in those who had subtotal thyroidectomy and radioiodine therapy, and 11% in those who had only partial thyroidectomy. In addition, in patients who develop pulmonary metastases, radioiodine therapy can be used more successfully when all thyroid tissue has been resected.[60,67]

An additional theoretical argument in favor of total thyroidectomy in papillary thyroid cancer is that histological evidence of multicentric bilateral disease is present in up to 80% of patients.[68] Although some report that these microscopic tumor foci have little clinical significance, others have shown that patients with multiple intrathyroid tumors are 2 times more likely to have nodal metastases and 3 times more likely to have pulmonary metastases and persistent disease.[50,69] Furthermore, Mazzaferri's data[49] suggested that multiple intrathyroidal tumors were an important prognostic factor, which increased the 30-year mortality rate. There is also the theoretical risk that a small-differentiated thyroid cancer can dedifferentiate into anaplastic thyroid cancer. Although this is an extremely rare occurrence, total thyroidectomy would obviate this possibility.

Proponents of a less-than-total or near-total thyroidectomy have argued that there is an increased risk of complications when performing total thyroidectomy. However, several authors have demonstrated that total thyroidectomy, when performed by experienced thyroid surgeons, can be accomplished with the same morbidity and mortality as a thyroid lobectomy.[61,70–72]

Optimal Surgery for Papillary Thyroid Carcinoma

The unresolved debate regarding the choice of operation for well-differentiated carcinoma of the thyroid has not and will not be resolved in the absence of appropriately designed trials. That considered, we performed a power study and analyzed the feasibility, scope, sample size, and length of follow-up required to determine the optimum operation for papillary carcinoma of the thyroid.[73] A statistical approach was used to design a randomized prospective trial that compared end points such as complications, recurrence, and cause-specific mortality. A comparison of complications is prohibitive, because of the large sample size required. Specifically, approximately 12,000 randomized patients would be needed for such a study. A trial analyzing the end point of recurrence seems feasible based on a more attainable sample size. In such a trial, between 360–800 patients would be needed and follow-up would require 6–10 years. However, an inherent bias would be present in such a trial because detection of recurrence would be severely compromised in the lobectomy arm; the use of radioiodine or serial thyroglobulin measurements would not be possible if an entire thyroid lobe remained in situ. Accordingly, a unilateral lag-time bias would occur in the lobectomy arm. Therefore, a cause-specific mortality trial is the least objectionable. Such a trial would require a sample size of approximately 3,100 patients. It could be performed in a multi-institutional setting; however, such a study would be challenging because of the long follow-up required and the inherent difficulties of working with multiple institutions in which disease management is likely to change.[73]

Surgeon Experience: Clinical and Economic Outcomes After Thyroidectomy

The debate about the appropriate operation for well-differentiated thyroid cancer has raged for years and is

unlikely to be resolved. What is clear, however, is that surgeon experience counts. This has recently been demonstrated in a large statewide retrospective analysis of the results of thyroid surgery.[72] A cross-sectional analysis of all patients who underwent thyroidectomy in Maryland from 1991 through 1996 was conducted, using a computerized statewide hospital discharge database. Surgeons were categorized into four groups by the volume of thyroidectomies they performed over this time period: group A performed 1–9, group B performed 10–29, group C performed 30–100, and group D performed more than 100. Multivariant statistical regression was used to assess the relationship between surgeon case load, hospital complications, length of stay, and total hospital charges, adjusting for case mix and hospital volume. The highest-volume surgeons performed the greatest proportion of total thyroidectomies and were more likely to operate on patients with cancer. Those surgeons also had the shortest length of stay and lowest complication rates. Length of stay and complication rates were determined by the experience of the surgeon, not by the volume of cases performed at individual hospitals. This association between surgeon volume and outcome does have important implications. The results suggest that 20% of the complications could have been prevented and 1700 hospital days could have been saved if all thyroidectomies had been performed by high-volume surgeons.[72]

Differentiated Thyroid Cancer: Adjuvant Radioiodine Therapy and Thyroid Hormone Suppression

Steven I. Sherman, MD

Once a patient with differentiated thyroid carcinoma has undergone surgical therapy, several possible adjuvant modalities can be considered depending on the patient's extent of disease. Unfortunately, data from prospective randomized clinical trials of these various therapies are generally lacking, and conclusions regarding the selection of treatment must be based on retrospective data. Similarly, the published standard guidelines for long-term follow-up of these patients leave considerable room for variation in the frequency and selection of monitoring procedures.[74]

Adjuvant Therapy

^{131}I, when concentrated in thyroid tissue, permits visualization of that tissue by scanning to detect the gamma radiation emitted by ^{131}I, and causes thyroid cell death by emission of short-path-length beta rays. Additionally, radioiodine uptake is dependent on adequate stimulation by TSH. After thyroidectomy, a patient's serum thyroid hormone concentration must decline sufficiently to allow the serum TSH concentration to rise above 25 mU/L, which typically takes 4–5 weeks.[75] To minimize the symptoms of this induced hypothyroidism, the shorter-acting hormone liothyronine (T3) can be given at a dose of 25 μg 2–3 times per day; lower doses should be given in elderly patients and those with ischemic heart disease.[76] After cessation of T3 therapy, the serum TSH concentration rises above 25 mU/L within 1–2 weeks. Another way to minimize hypothyroid symptoms in patients already taking thyroxine (T4) is to reduce the T4 dose by 50% for approximately 1 month rather than stopping T4 therapy entirely.[77] Whichever preparative regimen is used, serum TSH should be measured before any radioiodine is given to confirm that the concentration is sufficiently elevated.

Radioiodine scans for localization of uptake before ablation or therapy are usually performed using oral radioiodine doses of 2–5 mCi (74 to 185 MBq of ^{131}I).[78] Greater sensitivity for the detection of residual or metastatic tumor can be attained by using higher doses,[79,80] but higher doses can lead to "stunning," in which there is reduced uptake of the subsequent ablative or therapeutic dose due to sublethal radiation delivered in the diagnostic dose.[81,82] Between 24 to 96 hours after administration of the diagnostic dose, whole-body scans are performed with a large field-of-view gamma-scintillation camera fitted with a high-energy parallel hole collimator. Spot images of the neck and other areas of uptake can be obtained using either this equipment or a rectilinear scanner. Quantitative dosimetry can be performed to determine lesion uptake and predict an effective radiation dose, but this requires specialized equipment and software.[54] Between 75% and 100% of patients have radioiodine uptake in the thyroid bed after thyroidectomy. Metastatic disease in the lungs or in bone can also be frequently visualized on these scans. Certain histological subtypes, such as oxyphilic follicular carcinoma (commonly called Hurthle cell carcinoma), concentrate radioiodine less often. Older patients and women may also be less likely to have adequate uptake in metastases.[54,83]

In the absence of known residual or metastatic disease visualized on a low-dose radioiodine scan, adjuvant ablation of residual thyroid tissue after primary surgery has three purposes: (1) destroy any residual microscopic foci of carcinoma, (2) increase the sensitivity of radioiodine scanning for detection of recurrent or metastatic disease due to the elimination of uptake by residual normal thyroid tissue, and (3) improve the value of measurements of serum thyroglobulin as a tumor marker. Combining retrospective data from multiple studies, radioiodine ablation may be associated with as much as a 50% reduction in locoregional relapse; also, long-term disease-specific mortality is probably reduced in patients with primary tumors that are at least 1.0 to 1.5 cm in diameter, are multicentric, or have soft-tissue invasion at presentation.[49,51,84,85] Opinions about the value of adjuvant radioiodine ablation vary widely, but postoperative radioiodine should probably be administered to all patients with differentiated thyroid carcinoma who are age 45 or older at diagnosis, whose primary tumor was at

least 1.0–1.5 cm in diameter, or who have had histological evidence of extrathyroidal tumor extension, either by direct invasion outside the gland or locoregional soft tissue or lymph node metastases. In the presence of postoperative radioiodine uptake in the thyroid bed, 100 mCi of radioiodine is administered as an empiric dose, resulting in effective ablation in about 80% of patients.[86] A posttherapy scan is performed several days after administration of the radioiodine dose, and significant new foci of uptake are seen in up to 10% of patients.[82] When metastatic uptake is detected on the low-dose scan, higher doses (150–200 mCi) of radioiodine are administered. Alternatively, dosimetric calculations can permit individualization of the radioiodine doses necessary to ablate a thyroid remnant or treat metastatic disease.

Thyroid Hormone Suppression

After initial therapy consisting of surgery with or without radioiodine administration, patients require lifelong thyroid hormone treatment to prevent hypothyroidism and minimize TSH stimulation of tumor growth.[87] Several studies have suggested that thyroid hormone therapy improves survival, causing a 2- to 3-fold improvement in relapse-free survival associated with TSH suppression.[49,83,88,89] However, potential morbidity from overly aggressive thyroid hormone suppression therapy may include acceleration of osteopenia[90,91] and cardiac tachyarrhythmias.[92] Some studies have also suggested that TSH-suppressive therapy leads to induction of cardiac hypertrophy and dysfunction;[93–95] however, these findings have recently been disputed.[96,97] It seems most appropriate to treat patients with suppressive doses of T4 after initial therapy, and to base the degree of TSH suppression on the patient's initial clinicopathologic features and disease status during follow-up. I suggest the following guidelines:

- primary tumor <1 cm in diameter: maintain TSH within the lower half of the normal range;
- primary tumor >1 cm in diameter: maintain TSH between 0.1 and 0.5 mU/L;
- locoregional nodal disease: maintain TSH between 0.05 and 0.10 mU/L;
- extrathyroidal invasion or extracervical metastatic disease: maintain TSH below 0.05 mU/L.

Patients who remain disease-free for 5–10 years may have their degree of TSH suppression reduced by lowering their doses of thyroid hormone. Other mitigating factors, such as concurrent cardiac disease, may also dictate a need for reduced hormone doses.

Long-Term Follow-Up

Recurrence of differentiated thyroid carcinoma can occur decades after initial therapy, mandating the need for careful monitoring to detect and treat recurrence in order to reduce morbidity and mortality.[49] No single diagnostic tool can detect all recurrences; therefore, combinations of diagnostic modalities must be employed. In addition to radioiodine scans, routine monitoring can include measurement of serum thyroglobulin, chest radiographs, and cervical ultrasonography.

Radioiodine scanning is also valuable during the long-term follow-up of patients to detect recurrent or metastatic disease. After successful ablation therapy, the absence of residual iodine uptake in the thyroid bed or metastatic locations on two consecutive annual scans has a predictive value of 97% for 10-year recurrence-free survival.[98] Although T4 withdrawal has previously been required, exogenously administered r-TSH can now be substituted for endogenous TSH elevation.[57] Two intramuscular injections of 0.9 mg of thyrotropin 24 hours apart provide sufficient TSH stimulation to allow radioiodine scanning, although the diagnostic efficacy of such scanning is somewhat lower than after traditional hormone withdrawal.

Measurement of the serum concentration of thyroglobulin aids the detection of residual, recurrent, or metastatic disease, particularly given the rough correlation between tumor size and thyroglobulin level. The presence of a significant amount of residual normal thyroid tissue after surgery can reduce the reliability of thyroglobulin measurements. Once the thyroid gland has been resected and completely ablated using radioiodine, the serum thyroglobulin concentration should approach the limits of assay detectability.[99] During follow-up, the thyroglobulin level may take 1 or more years to decline to an undetectable nadir after primary therapy.[100] Given the dependence on TSH for thyroglobulin production, one important factor in the interpretation of thyroglobulin concentration is the concurrent level of TSH. Thus, the sensitivity for detection of residual cancer is only about 50% during TSH-suppressive T4 therapy but may be as high as 85% to 90% after T4 withdrawal and TSH elevation.[55,100–102] False-negative results can occur, however, particularly in patients with small lymph node metastases from papillary carcinoma or in the setting of tumor dedifferentiation. Whereas a detectable thyroglobulin level, even during TSH-suppressive thyroid hormone therapy, likely signifies disease, the absence of detectable thyroglobulin during TSH stimulation suggests the absence of disease. After r-TSH injections, the combination of radioiodine scanning and thyroglobulin

determination yields adequate diagnostic sensitivity for metastatic disease to permit its substitution for T4 withdrawal scans during long-term follow-up.

In immunometric assays, reported thyroglobulin concentrations can be falsely lowered by autoantibodies that bind thyroglobulin and prevent antigen interaction with the assay's antibodies.[103] For the 25% of patients with differentiated thyroid cancer who have antithyroglobulin autoantibodies, the serum thyroglobulin level must be interpreted with caution or not used at all in disease management. Notably, the persistence of antithyroglobulin autoantibodies in a differentiated thyroid cancer patient after thyroidectomy and radioiodine ablation likely indicates the presence of residual thyroid tissue and may predict an increased risk of recurrence.[104] Use of sensitive polymerase chain reaction methods that detect thyroglobulin messenger RNA circulating in the peripheral blood of patients with thyroid cancer, presumably contained within circulating tumor cells, may bypass the problem of antithyroglobulin antibodies interfering with immunoassay techniques.[105]

Ultrasonography of the thyroid bed and cervical lymph node compartments can accurately identify locoregional metastases and disease recurrence measuring only several millimeters in diameter.[106] Additionally, identification of suspicious lesions can be followed by ultrasound-guided FNA. For example, in one study, 50% of patients with locoregional disease diagnosed using high-resolution ultrasonography had undetectable thyroglobulin levels and 80% had negative radioiodine scans.[107] Ultrasonography should be used as part of the follow-up of patients with lymph node metastases or extrathyroidal tumor extension at initial presentation. Computed tomography is probably not as sensitive in detecting such small recurrences, but the technique is more readily standardized and less operator-dependent than ultrasonography. Routine chest radiographs have limited sensitivity, particularly in the setting of micronodular metastases, but may identify macronodular metastases that do not concentrate radioiodine. Other imaging modalities may be beneficial in evaluating patients with elevated or rising thyroglobulin levels, such as scintigraphy with 111-indium-DTPA-Phe-octreotide,[108] ^{99m}Tc-tetrofosmin,[109] or 201-thallium;[110] positron emission tomography; and magnetic resonance imaging. Given the propensity of follicular thyroid carcinoma to metastasize to bone, skeletal imaging with ^{99m}Tc-pyrophosphate may also be of value.

In summary, individual clinicopathologic features may allow development of a routine follow-up strategy, as follows:[111]

- Years 1–3: clinical examination and serum free-T4, TSH, and thyroglobulin estimation every 6 months; chest radiography, cervical ultrasonography, radioiodine scanning and potential therapy annually (after T4 withdrawal or r-TSH injections) until two successive negative scans are done (every 6 months in patients with extracervical disease).
- Years 4–10: clinical examination, serum free-T4, TSH, thyroglobulin level, and chest radiography annually; neck ultrasonography every 2 years; radioiodine scanning if a rising thyroglobulin level or recurrence is detected.
- Years 11–20: clinical examination and serum free-T4, TSH, and thyroglobulin level annually; chest radiography and neck ultrasonography every 3 years; radioiodine scanning if a rising thyroglobulin level or recurrence is detected.
- Years 21+: clinical examination and serum free-T4, TSH, and thyroglobulin level annually; chest radiography and neck ultrasonography every 3–5 years; and radioiodine scanning if a rising thyroglobulin level or recurrence is detected.

Hurthle Cell Neoplasms

Norman W. Thompson, MD

In 1894, Hurthle described an interfollicular cell of the thyroid gland found in a normal dog and noted that Baber had previously described the same cell in the thyroid of a variety of laboratory animals.[112] In fact, Hurthle had described the parafollicular C cell in the dog but not the cell that subsequently became associated with his name. Instead, it was Ewing who, when describing a thyroid tumor in 1928, credited Hurthle with the original description of its cell type and as a result called this lesion a "Hurthle cell tumor".[113] To complicate this situation further, the tumor described by Ewing had previously been described by Langhans and was composed of a different cell than that described by Hurthle.[114] This distinct cell was originally described by Askanazy.[115] Therefore, to be precise, we should call Hurthle cell tumors either Askanazy-cell or Langhans tumors. The characteristic cells in these tumors are morphologically similar to those occurring in other organs, such as the salivary glands, parathyroid glands, and kidney; these cells have been referred to as oncocytes, and their tumors have been referred to as oncocytomas.

Hurthle cell thyroid tumors are composed of large, frequently polygonal eosinophilic cells with an abundance of fine granular cytoplasm. The Hurthle cell is a distinctive oxyphilic cell filled with cytoplasmic mitochondria. Such cells are also frequently found in thyroid glands with lymphocytic thyroiditis, Graves' disease, nodular goiters, and surrounding well-differentiated carcinomas. These cells have round to oval nuclei that are larger than the nuclei of normal follicular cells. They often contain one or more nucleoli, intranuclear cytoplasmic invaginations, and single or multiple homogeneous electron-dense bodies within the mitochondrial matrix. The Hurthle cell is generally believed to arise, from or be a variant of, follicular cells within the thyroid gland. The evidence that Hurthle cell tumors are of follicular-cell origin includes histological studies demonstrating numerous transition forms between follicular and Hurthle cells within the same thyroid gland, the presence of thyroglobulin immunoreactivity (but none for thyrocalcitonin), and a higher concentration of Hurthle cells in stimulated and inflammatory thyroid tissue than in normal thyroid tissue.[113,116–118] Also, it has been demonstrated that there is a functional TSH receptor-adenylate cyclase system in benign Hurthle cell neoplasms.[119]

Despite the fact that Hurthle cell neoplasms may be closely related to other well-differentiated neoplasms of the thyroid, we feel that they should be classified as a distinct entity in that their biologic behavior is different from that of follicular neoplasms. In our experience, the incidence of metastasis of Hurthle cell tumors to lymph nodes and either multicentricity or intraglandular lymphatic spread is higher than that in follicular cancers.[113,120] Furthermore, true Hurthle cell carcinomas fail to concentrate radioiodine sufficiently to be imaged or treated. Despite the differences noted above, there are many classifications of thyroid neoplasms that include Hurthle cell tumors as a variant of follicular neoplasms. Furthermore, the nomenclature is not standardized, because Hurthle cell tumors are also referred to as oncocytomas, oxyphilic tumors, and follicular neoplasms with Hurthle cell change. In 1988, the World Health Organization formally classified Hurthle cell carcinoma as an oxyphilic variant of follicular carcinoma. A number of groups, however, are convinced that it should be classified separately as a Hurthle cell neoplasm.[113,120–123]

Diagnosis

The presence of a large collection of Hurthle cells (nodule) within a thyroid gland does not necessarily imply that it is a true neoplasm. Benign Hurthle cell nodules can be associated with other nonneoplastic inflammatory conditions, such as thyroiditis, Graves' disease, and colloid-nodular thyroid lesions. The presence of multiple nodules composed of Hurthle cells without encapsulation and found in association with these diseases represents a nonneoplastic, inflammatory, or reactive process. This type of nodule has no neoplastic potential but should always be considered in the differential diagnosis when an FNA of a thyroid nodule shows only Hurthle cells. There has been considerable controversy regarding whether reliable criteria existed for differentiating between benign and malignant Hurthle cell neo-

plasms.[116,120–122,124–126] There are no specific immunohistochemical markers or features seen on electron microscopy that permit one to distinguish between benign and malignant Hurthle cell tumors.[117] Cellular atypia expressed as the nuclear size and degree of anisokaryosis is not a relevant criterion. Aneuploidy has been noted in both benign and malignant tumors; however, several studies have shown that the presence of aneuploid nuclear DNA content in a Hurthle cell neoplasm is associated with an increased risk of recurrence, distant metastases, and death. Diploid nuclear DNA content is associated with a benign clinical course, even when other criteria for malignancy are present.[116,127–130]

The role of FNA biopsy in establishing the diagnosis of Hurthle cell lesions has been addressed in a number of studies.[118,125,131] In summary, these all show that the distinction between benign and malignant Hurthle cell neoplasms based on cytopathology alone probably cannot be made with a high degree of accuracy. Hurthle cell lesions, like follicular lesions of the thyroid diagnosed using FNA biopsy, require careful histopathologic evaluation before concluding whether they are benign or malignant. The diagnosis of a Hurthle cell neoplasm using FNA biopsy should be followed by a thyroid lobectomy and isthmectomy, as well as a more extensive procedure, when appropriate, based on final histopathologic studies.

Clinical Features

The peak age of incidence of Hurthle cell neoplasms is in the 5th and 6th decades of life. Patients with Hurthle cell carcinoma tend to be older than those with other Hurthle cell neoplasms, with the peak age of incidence in the 7th and 8th decades of life. The majority of patients ($\geq$60%) present with a solitary thyroid mass, which is most frequently nonfunctioning on thyroid scintigrams. Approximately 30% of patients with Hurthle cell carcinomas have a history of pre-existing or coexisting nonmalignant thyroid disease, including nontoxic nodular goiter, Graves' disease, toxic nodules, or subacute thyroiditis. Also, well-differentiated thyroid carcinomas have been found within the resected thyroid glands in approximately 40% of patients with Hurthle cell neoplasms. These consisted of small papillary carcinomas (79%) and follicular carcinomas (20%). It should be noted, however, that most of these patients had undergone previous head and neck irradiation. Overall, the incidence of previous head and neck irradiation in various reports of Hurthle cell neoplasms ranges from 7–39%, which strongly suggests that irradiation may be a predisposing factor in the development of Hurthle cell neoplasms.[113,120,122–124,132,133]

Seventy to eighty percent of patients with Hurthle cell carcinomas will have disease confined to the thyroid gland, 11% will present with lymph node metastases, and approximately 15% will present with distant metastases. The association between tumor size and malignancy in Hurthle cell neoplasms remains unclear; we previously regarded all Hurthle cell neoplasms larger than 2 cm in diameter as possibly malignant.[120] However, subsequent review of 12 consecutive Hurthle cell neoplasms $\geq$ 4 cm in diameter revealed that 80% were malignant as determined by the presence of capsular or vascular invasion.[113]

Surgical Management

Twenty-eight percent of all Hurthle cell neoplasms are malignant.[113] Therefore, we currently recommend that any patient with an FNA biopsy sample that demonstrates a predominance of Hurthle cells undergo a thyroid lobectomy and isthmectomy for a definitive diagnosis. If gross and/or microscopic (frozen-section) analysis show Hurthle cell nodules in association with Hashimoto's thyroiditis, colloid nodular goiter, or any other benign process, then the procedure should be terminated. When a true Hurthle cell neoplasm (encapsulated tumor composed of Hurthle cells) has been identified using frozen-section analysis, several extra sections should be taken through the capsule and evaluated carefully for the presence of either vascular or capsular invasion. If none of the accepted criteria for malignancy are demonstrated and the contralateral lobe is grossly normal, the procedure should be terminated with the understanding that a definitive diagnosis must await permanent histopathologic analysis. If a subsequent diagnosis of Hurthle cell carcinoma is made, a completion total thyroidectomy should be performed within a few days of the initial procedure. However, there are several exceptions to these policy guidelines. First, if the patient has a history of previous head and neck irradiation, we frequently proceed with a total thyroidectomy, even when the pathologist cannot determine whether the Hurthle cell neoplasm is benign or malignant at the time of frozen-section analysis. This is because such patients frequently have multicentric disease, including concomitant papillary carcinoma. Second, in patients with a palpable nodule in the contralateral lobe, but without a colloid goiter, we also frequently complete the total thyroidectomy in one stage. Finally, although tumor size cannot be directly correlated with malignancy, the majority of Hurthle cell carcinomas are $\geq$4 cm in diameter. Because many of the

true Hurthle cell neoplasms of that size or larger show capsular or vascular invasion after careful histological review, we consider tumor size a factor in determining whether to proceed with a total thyroidectomy. Although tumor size is a relative indication for total thyroidectomy that is currently used on an individual basis (and with the preoperative informed consent of the patient), total thyroidectomy has avoided the need for reoperation in the majority of our patients with lesions >4 cm in diameter.

When a Hurthle cell carcinoma has extended into contiguous structures, every effort is made to totally excise all gross tumor. Perithyroidal lymph nodes should be carefully sampled, and if positive for carcinoma, regionally resected (central compartment). If jugular nodes are grossly involved, a modified radical neck dissection is indicated.[113] Although lymphatic metastases from follicular carcinoma are unusual in all but advanced cases, Hurthle cell carcinomas may spread via lymphatics to cervical and/or anterior mediastinal lymph nodes in the absence of hematogenous spread; such disease may still be cured if surgery includes an appropriate regional lymphadenectomy.

Radioiodine and Metastatic Disease

One of the features that distinguishes Hurthle cell carcinoma from follicular carcinoma has been its apparent inability to concentrate radioiodine. Our previous experience in attempting to image or treat known metastatic Hurthle cell carcinomas led us to the conclusion that such tumors rarely, if ever, take up sufficient radioiodine for it to be therapeutic.[113,120] As a result, we have not subjected patients who have this diagnosis to a prolonged period of thyroid hormone deprivation and subsequent scintigraphy unless a distant metastasis has been detected using other types of imaging. Nevertheless, we and others have found that the majority of Hurthle cell carcinomas are capable of synthesizing thyroglobulin. Because of the limited therapeutic options available for patients with distant metastases from Hurthle cell carcinomas, scintigraphy should be considered after thyroid deprivation in such cases, particularly if the serum thyroglobulin level is markedly elevated.[113,120,121,123,124,132] For example, in one report of two cases of Hurthle cell carcinoma, distant metastases were shown to accumulate radioiodine. In patients whose tumor biopsy immunohistochemical stain shows thyroglobulin within tumor cells and who have an elevated serum thyroglobulin level, radioiodine scintigraphy should be performed 6 weeks after thyroid hormone administration is discontinued. Thus far, there has been no reported experience using r-TSH in patients with Hurthle cell neoplasms, which would alleviate the morbidity of prolonged hypothyroidism in a situation in which the benefit is likely to be very small. With the use of r-TSH scanning, if the scan were positive, only then would thyroid deprivation be initiated in preparation for radioiodine therapy.

External-beam irradiation is useful in patients who have painful bone metastases, but it is certainly not curative. In patients with isolated bone metastasis, particularly in a long bone, surgical resection should be considered. The use of either single-agent or combinations of chemotherapy in patients with metastatic disease has been universally disappointing.

The Surgical Treatment of Familial Medullary Thyroid Carcinoma

Jeffrey F. Moley, MD

Definition and Clinical Presentation

Medullary thyroid carcinoma (MTC) arises from the thyroid C cells. These are neuroendocrine cells that secrete the hormone calcitonin. MTC accounts for approximately 5–9% of all thyroid cancers seen in the United States. Approximately 75% of MTCs are sporadic, and 25% occur in hereditary settings. MTC is the predominant feature of the multiple endocrine neoplasia (MEN) type 2 syndromes, which include MEN 2A, MEN 2B, and familial non-MEN medullary thyroid carcinoma (FMTC).[134] These are autosomal dominant inherited syndromes that are caused by germ line mutations in the RET proto-oncogene. In these syndromes, MTC is multifocal and bilateral and occurs at a young age. In patients affected by MEN 2A, MEN 2B, or FMTC, there is almost complete penetrance of MTC: all individuals who inherit the disease allele develop MTC. Other features of the syndromes are variably expressed with incomplete penetrance. These features are summarized in Table 4.

In MEN 2A, all patients develop multifocal, bilateral MTC and C-cell hyperplasia. Approximately 42% of affected patients develop pheochromocytomas, which may also be multifocal and bilateral. Hyperparathyroidism develops in 25–35% of patients and is caused by hyperplasia. Cutaneous lichen amyloidosis and Hirschsprung's disease are infrequently associated with MEN 2A. In MEN 2B, 40–50% of patients develop pheochromocytomas, and all patients develop neural gangliomas, particularly in the mucosa of the digestive tract, conjunctiva, lips, and tongue. MEN 2B patients also have megacolon, skeletal abnormalities, and markedly enlarged peripheral nerves. However, MEN 2B patients do not develop hyperparathyroidism. MTC in MEN 2B patients develops during infancy and appears to be the most aggressive form of hereditary MTC. Finally, in FMTC, patients develop MTC without any other endocrinopathies. In these patients, MTC has a later age of onset and a more indolent clinical course than in patients with MEN 2A or MEN 2B. Occasionally, FMTC patients will never manifest clinical evidence of MTC (symptoms or a lump in the neck) even though biochemical testing and histological evaluation of the thyroid indicates MTC.

Calcitonin is a specific tumor marker for MTC. It is extremely useful in the screening of individuals predisposed to the hereditary forms of the disease and in the follow-up of patients who received treatment. C cells also secrete other hormones, including carcinoembryonic antigen (CEA), which is also useful in the follow-up of patients with MTC.

Hereditary MTC and Preventive Thyroidectomy

In 1993, point mutations associated with MEN 2A and FMTC were identified in the RET proto-oncogene, which encodes a transmembrane protein tyrosine kinase receptor.[135,136] These mutations usually result in the nonconservative substitution of a cysteine residue in exons 10, 11, 13, 14, or 15, although other amino acid changes have been

TABLE 4. *Clinical features of sporadic MTC, MEN 2A, MEN 2B, and FMTC*

Clinical setting	Features of MTC	Inheritance pattern	Associated abnormalities	Genetic defect
Sporadic MTC	Unifocal	None	None	Somatic RET mutations in >20% of tumors
MEN 2A	Multifocal, bilateral	Autosomal dominant	Pheochromocytoma hyperparathyroidism	Germline missense mutations in extracellular cysteine codons of RET
MEN 2B	Multifocal, bilateral	Autosomal dominant	Pheochromocytoma, mucosal neuromas, megacolon, skeletal abnormalities	Germline missense mutation in tyrosine kinase domain of RET
FMTC	Multifocal, bilateral	Autosomal dominant	None	Germline missense mutations in extracellular or intracellular cysteine codons of RET

found. In MEN 2B, a single mutation in exon 16 (codon 918) is present, although in one family, a codon 883 mutation has been described. The mutations have been shown to result in gain of function in the RET protein product, with increased intrinsic tyrosine kinase activity and/or alterations of substrate recognition, and transforming capability.

Individuals with MEN 2A, MEN 2B, and FMTC are virtually certain to develop MTC at some point in their lives (usually before 30 years of age). Therefore, at-risk family members who have inherited an RET gene mutation are candidates for thyroidectomy regardless of their stimulated plasma calcitonin level. In children with nonpalpable disease detected by genetic screening, lymph node metastases are rarely present, and the calcitonin level is normalized postoperatively in the majority of patients. At our institution, we have performed 67 preventive thyroidectomies in RET mutation carriers.[137] Forty-three of these patients had a normal preoperative stimulated calcitonin level. Postoperative calcitonin levels remained normal in all patients except one who had MEN 2B.

Surgical Management

Cases of hereditary MTC not detected by genetic screening and most cases of sporadic MTC present as a neck mass detected on physical exam. Surgical treatment of established MTC is influenced by several factors. First, the clinical course of MTC is usually more aggressive than that of differentiated thyroid cancer, with higher recurrence and mortality rates. Second, MTC cells do not take up radioiodine, and external-beam radiotherapy and chemotherapy for MTC are largely ineffective. Third, MTC is multicentric in 90% of patients who have the hereditary forms of the disease and 20% of patients who have the sporadic form. Fourth, the majority of MTC patients with palpable disease have lymph node metastases. Lastly, the ability to measure postoperative stimulated calcitonin levels in MTC patients has allowed assessment of the adequacy of surgical extirpation. Consequently, it has been found that thorough surgical extirpation is the only curative treatment of MTC. Total thyroidectomy is the appropriate treatment for the primary tumor, accompanied by a lymph node dissection. In a recent report of lymph node involvement in patients with palpable MTC, we found that the incidence of central (levels VI and VII) lymph node metastases was extremely high (79%) regardless of the size of the primary tumor.[138] There was also frequent involvement of ipsilateral (75%) and contralateral (47%) level II, III, and IV lymph nodes, which supports our recommendation that these lymph nodes be removed routinely in patients with palpable MTC. We also recommend that parathyroidectomy with autotransplantation be performed at the time of primary surgery for MTC. We do this for two reasons. First, it is usually not possible to perform a thorough central neck dissection and preserve the parathyroids. Second, if the patient requires reoperation for recurrence in the central neck, the parathyroids are not jeopardized if they have been autotransplanted.

Surgical Management of Residual or Recurrent Disease

After primary surgical treatment, the calcitonin level remains elevated in over 50% of patients who present with palpable MTC. We have demonstrated liver metastases by laparoscopy in 25% of these patients, despite their having normal livers on CT or MRI.[139] In patients with no evidence of distant metastases, we often re-explore the neck if there is evidence of tumor remaining in the neck or if residual thyroid and nodal tissue remain in the central and lateral neck compartments. This operation, which has been termed microdissection by Tisell and others, has resulted in normalization of the stimulated calcitonin level in one-third of patients.[140] Between August 1992 and November 1996, we evaluated 115 patients who had recurrent or persistent calcitonin-level elevation after primary surgery for MTC.[141] Sixty-two of the 115 patients (54%) underwent surgery. In 10 (16%) of these 62 patients, laparoscopic or open examination revealed liver metastases. In seven (11%) patients, palliative debulking of cervical tumor was carried out. In the remaining 45 patients, 51 operations were carried out with curative intent. Reoperative central dissection of level VI and VII lymph nodes was done in all patients. Bilateral (30 patients) or unilateral (15 patients) functional neck dissection (level II, III, IV, and V lymph nodes) was also carried out. The mean decrease in stimulated calcitonin level after surgery was 73.1%. In 22 of 45 patients (49%), the postoperative stimulated calcitonin level dropped more than 90% below the preoperative value. Seventeen (38%) patients had a postoperative stimulated calcitonin level within the normal range; the remaining patients had a $>$35% reduction in the stimulated calcitonin level. These results indicate an improvement in outcome from reoperation compared with those of our previous series.[141,142] This improvement has occurred mainly because of improved preoperative selection of patients, including routine preoperative laparoscopic liver examination, which in our study identified metastases in 10 patients, 9 of whom had normal CT and MRI of the liver.

The Surgical Treatment of Sporadic Medullary Thyroid Carcinoma

Douglas B. Evans, MD

Large institutional and cooperative-group studies of MTC have demonstrated that the stage of disease at diagnosis most accurately predicts length of survival.[143–145] In the absence of metastatic or progressive, unresectable local-regional disease, long-term survival (≥10 years) is common (60%–90%). In contrast, MTC patients with metastatic disease have a 5-year survival rate of approximately 50%. Similar to the case with differentiated carcinoma of the thyroid, factors associated with an increased rate of MTC recurrence and decreased survival duration include advanced age, extracapsular (thyroid) tumor extension, progression of cervical lymph node metastases to the mediastinum, extranodal tumor extension, and incomplete surgical resection of the primary tumor and adjacent lymph node metastases. In contrast to patients with papillary carcinoma of the thyroid, the presence or absence of these prognostic variables does not mandate specific adjuvant treatments. This is because radioiodine ablation and thyroid suppression are ineffective therapies for MTC. The use of external-beam irradiation remains controversial owing to its toxicity profile and the conflicting evidence in support of its efficacy.[146,147]

The management of MTC is further complicated by our ability to measure serum levels of calcitonin and CEA, which are highly sensitive markers of persistent or recurrent disease. Unlike with other solid tumors, it is possible to detect MTC by measuring the calcitonin or CEA level at a stage when there is no disease detectable using any other technique. There is general agreement that individuals with detectable calcitonin after resection of the primary tumor have residual MTC. However, there are no data to accurately predict what percentage of patients with detectable calcitonin or CEA will develop identifiable metastases and what percentage will die of metastatic disease. It remains impossible to accurately predict the course of MTC in patients with nonmetastatic disease based on the calcitonin level after thyroidectomy.[148] Despite the often indolent course of MTC, management is complicated by the frequent progressive rise in the calcitonin level seen during outpatient follow-up. The absence of prospective, long-term follow-up data on patients with an elevated postoperative calcitonin level (without measurable distant-organ metastatic disease) has contributed to the controversy over appropriate treatment (as discussed by Dr. Moley).

MTC is characterized by early spread to regional lymph nodes.[149] It is likely that the majority of patients with invasive MTC have metastasis to regional lymph nodes at the time of diagnosis. This is supported by the frequent finding of persistent elevations of the calcitonin level after primary tumor resection (thyroidectomy) and the high rates of cervical recurrence (in regional lymph nodes) reported in retrospective studies (21–65%). These data have provided the rationale for surgeons to perform a more extensive lymphadenectomy at the time of initial thyroidectomy. Dralle et al.[150] coined the term "compartment-oriented cervical lymphadenectomy" for the removal of lymph nodes from anatomically defined compartments. Distant metastases occur in the liver, lung, bone, and occasionally, brain. Similar to metastases from other neuroendocrine tumors, liver metastases are poorly visualized using CT and are best seen using MRI or good-quality ultrasonography. The frequency at which early-stage MTC spreads to the liver and other extracervical sites is unknown. Data allowing one to correlate the extent of cervical disease and calcitonin-level elevation with the likelihood of subclinical distant-organ metastases does not exist. Diagnostic techniques such as hepatic-vein sampling after pentagastrin stimulation and scintigraphy using anti-CEA monoclonal antibodies or octreotide may allow identification of patients with subclinical extracervical metastases. The extent of cervical surgery could then be based on the presence or absence of metastatic disease.

Surgical Treatment

The majority of patients who have a diagnosis of sporadic MTC first receive medical attention when a dominant thyroid nodule is discovered on physical examination. The diagnosis of MTC is accurately estab-

lished using FNA cytology in which the tumor-cell cytoplasm stains positively with calcitonin antiserum. All patients with a preoperative diagnosis of MTC should be screened for pheochromocytoma via 24-hour urine collection for metanephrine, vanillylmandelic acid, and free catecholamines, and blood should also be drawn for DNA testing (RET proto-oncogene analysis). We use cervical ultrasonography to assess the central and lateral neck, as well as the supraclavicular region for the presence of lymph node metastases. In patients with a palpable primary tumor or evidence of regional lymph node metastases, a metastatic survey should be performed that includes CT of the chest, MRI of the liver, and radionuclide bone scanning.

The majority of MTC patients (75%) have the sporadic form of the disease. We advocate an aggressive treatment approach for this disease based on published data that demonstrate improved local-regional disease control and suggest improved survival in patients who undergo compartment-oriented lymphadenectomy at the time of total thyroidectomy.[150–152] Therefore, in patients with a palpable thyroid nodule diagnosed as MTC by using FNA cytology, we perform a total thyroidectomy with in-continuity clearance of the central neck and a standard modified radical neck dissection on the side of the lesion.[153] Central neck dissection is defined as the removal of all fibrofatty and lymphatic tissue from the level of the hyoid bone down to the innominate vessels. An adequate dissection requires full mobilization of the sternohyoid muscles and resection of the underlying sternothyroid muscles. This resection is necessary to adequately expose the deep central neck at the level of the thoracic inlet. All soft tissue and lymphatics between the recurrent laryngeal nerve and trachea should also be removed; the upper aspect of the thymus is removed with the paratracheal lymph nodes. The lateral limits of the dissection are the internal jugular veins. The inferior parathyroids are usually inseparable from the cluster of lymph nodes and thymic horn that extends from the lower pole of the thyroid gland just inferior and anterior to the junction of the inferior thyroid artery and recurrent laryngeal nerve. Therefore, a standard central neck dissection often involves removal of the inferior parathyroid glands. These should be identified when possible, confirmed histologically (so as not to autograft a lymph node metastasis), and autografted into either the sternocleidomastoid muscle in the neck or the brachioradialis muscle in the nondominant forearm.

Total thyroidectomy and central neck dissection are safely performed in MTC patients who have not had previous cervical surgery. The incidence of permanent hypoparathyroidism and/or palsy of the recurrent laryngeal nerve in these patients should be no $>$1–2%. However, when they do occur, these complications significantly impact the quality of life and are obvious to both the surgeon and endocrinologist. The potential for such visible complications combined with the known indolent biologic behavior of MTC is likely responsible for the inadequate lymphadenectomies (at least in the central neck compartment) that accompany many thyroidectomies performed for this disease. It has been clearly demonstrated that compartment-oriented systematic lymphadenectomy decreases the local-regional recurrence rates and may improve length of survival in MTC patients.[150,151]

Because of the high incidence of subclinical lymph node metastases in the ipsilateral jugular chain, ipsilateral modified radical neck dissection is performed at the time of thyroidectomy in all patients with sporadic MTC even if there is no clinical or radiographic evidence of lymph node metastases. Modified radical neck dissection uses as its limits of dissection the posterior belly of the digastric muscles superiorly, the 11th nerve posterolaterally, and the clavicle and thoracic inlet inferiorly. The sternocleidomastoid muscle, jugular vein, carotid artery, and vagus nerve are skeletonized and preserved, and the omohyoid muscle is resected with the specimen. Data from our institution have demonstrated that lymph node metastases in the central neck and ipsilateral jugular chain are present in almost all patients with a grossly evident MTC, regardless of size, at the time of diagnosis.[153] Contralateral cervical lymph node metastases are present in at least one-third of patients with measurable primary tumors. Importantly, one can only assess the incidence of lymph node metastasis by performing anatomically defined, compartment-oriented lymphadenectomy followed by careful pathologic analysis. Classifying patients as node-positive or -negative after thyroidectomy, which may or may not have included some form of lymphadenectomy, artificially understages the disease in many patients.

The extent of primary surgery for MTC should also be based on the anticipated plan for postoperative follow-up and management. For example, the vast majority of patients with a palpable ($>$1 cm) primary tumor will have a persistent postoperative elevation in calcitonin level if a central compartment lymphadenectomy is not performed at the time of thyroidectomy. The postoperative calcitonin level is routinely measured during follow-up and invariably continues to rise slowly. Because of increasing patient and physician anxiety, often prompting multiple radiologic studies, MTC patients are referred for a second opinion regarding the potential benefit of reoperative cervical lymphadenectomy. How-

ever, patients who have undergone adequate (compartment-oriented) initial surgery need to be considered for reoperative cervical procedures only in the presence of documented recurrent disease, as seen by the use of imaging studies.

Adjuvant External-Beam Radiotherapy

Adjuvant external-beam radiotherapy should be considered for MTC patients who have a high risk of local-regional tumor recurrence after maximal surgical therapy. Although prospectively acquired data are lacking, postoperative external-beam radiotherapy should be considered for patients with positive surgical margins of excision, extranodal soft tissue extension, and extensive mediastinal tumor extension (often requiring median sternotomy). In such patients, tumor recurrence in the central neck compartment or anterior mediastinum would result in invasion of the trachea and/or esophagus, causing loss of speech and/or swallowing. However, external-beam radiotherapy should not be used as a replacement for surgical excision in MTC patients who have potentially resectable recurrent or locally advanced cervical disease. The radiotherapy treatment field extends from the mastoid to approximately the carina based on the individual clinical situation. AP/PA fields are used to deliver approximately 44 Gy (spinal cord tolerance $<$45 Gy) at a rate of 2 Gy per fraction; the total dose is taken to 60 Gy with a boost to the region that is at the highest risk of recurrence.

Brierley and colleagues[146] recently reported on the use of adjuvant cervical external-beam radiotherapy in high-risk MTC patients who were defined as those who have microscopic residual disease, lymph node metastasis, or extraglandular tumor invasion; patients with gross residual disease were excluded. Twenty-five patients received postoperative external-beam radiotherapy, and 15 patients received surgery alone. The local-regional recurrence rate was 14% in patients who received postoperative adjuvant radiotherapy compared with 48% in those who received surgery alone. Brierley and colleagues[146] were the first to recommend postoperative adjuvant external-beam radiotherapy in patients with an elevated calcitonin level after adequate cervical surgery. Their suggested radiotherapy program encompasses cervical, supraclavicular, and upper mediastinal lymph node distribution to a total dose of 40 Gy; patients who had microscopically positive surgical margins then received a 10-Gy boost. This more liberal application of external-beam irradiation in MTC patients warrants further consideration; however, patient numbers are likely to be too small to conduct a randomized clinical trial.

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