

Treatment Guidelines for Patients With Thyroid Nodules and Well-Differentiated Thyroid Cancer

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A set of minimum clinical guidelines for use by primary care physicians in the evaluation and management of patients with thyroid nodules or thyroid cancer was developed by consensus by an 11-member Standards of Care Committee (the authors of the article) of the American Thyroid Association, New York, NY. The participants were selected by the committee chairman and by the president of the American Thyroid Association based on their clinical experience. The committee members represented different geographic areas within the United States, to reflect different practice patterns. The guidelines were developed based on the expert opinion of the committee participants, as well as on previously published information. Each committee participant was initially assigned to write a section of the document and to submit it to the committee chairman, who revised and assembled the sections into a complete draft document, which was then circulated among all committee members for further revision. Several of the committee members further revised and refined the document, which was then submitted to the entire membership of the American Thyroid Association for written comments and suggestions, many of which were incorporated into a final draft document, which was reviewed and approved by the Executive Council of the American Thyroid Association.

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Between 4% and 7% of individuals in the United States have palpable thyroid nodules.^[1] Thyroid nodules are more common in women and increase in frequency with age. Fewer than 10% of solitary nodules are malignant. The physician who encounters a patient with a thyroid nodule must be able to determine its clinical significance, especially with regard to possible malignancy, compression of structures of the neck, or thyroid dysfunction. In this document, important elements of the history, physical examination, and laboratory evaluation are reviewed, and a suggested management strategy is presented. This outline is not intended to be all-inclusive, nor does it preclude additional evaluation, according to the specific clinical situation.

THYROID NODULES AND CANCER

HISTORY

Unfortunately, the history is neither sensitive nor specific in detecting underlying malignancy. However, the development of hoarseness, progressive dysphagia, or shortness of breath suggests growth or invasiveness, and it should raise the index of suspicion of malignancy. Prior irradiation for such conditions as thymic or tonsillar enlargement, or acne, as well as a family history of thyroid cancer predisposes to cancer. Male sex, in general, and nodules that appear in individuals younger than 20 years or older than 60 years, in particular, are additional risk factors for malignancy. The following elements of the history would suggest a benign process: a sudden or gradual onset of pain or tenderness (that would suggest either hemorrhage into a benign adenoma or cyst, or subacute granulomatous thyroiditis, respectively); symptoms of hypothyroidism (suggesting chronic autoimmune [Hashimoto] thyroiditis); and a family history of benign thyroid nodular disease, Hashimoto thyroiditis, or other autoimmune disease. However, thyroid cancer may occasionally be painful or tender.

PHYSICAL EXAMINATION

A physical examination that is relevant to the clinical situation should be performed. The pulse rate and blood pressure should be obtained, since a rapid pulse rate may suggest hyperthyroidism, and hypertension may occur in the context of multiple endocrine neoplasia, type II (MEN II). The neck should be carefully palpated for regional lymphadenopathy. While the presence of ipsilateral enlarged lymph nodes strongly suggests thyroid cancer, their absence in no way rules out malignancy. A smooth, soft,

easily mobile nodule suggests benignancy, as does the presence of tenderness. Deviation of the trachea, which suggests a mass, should be noted. The thyroid gland should be carefully palpated, and the location, size, consistency, and mobility of the nodule(s) and the presence or absence of tenderness should be noted. A firm to hard, irregular, fixed, nontender nodule is more likely to be a thyroid malignant neoplasm, although some thyroid cancers are smooth and not particularly hard; conversely, some benign nodules can be very hard because of calcifications.

Multinodularity, especially if the nodules all have the same consistency, is consistent with a benign multinodular goiter. A nodule or mass that is dominant in size or has a different consistency than other nodules within the gland should be evaluated by employing the same criteria as those outlined for single nodules. A midline nodule over the hyoid bone that moves up with protrusion of the tongue is likely to be a thyroglossal duct cyst.

LABORATORY EVALUATION

Fine-needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) has become the cornerstone in the evaluation of solitary thyroid nodules and dominant nodules within multinodular goiters.[1] It is a procedure that requires skill and experience by the individual who performs the procedure, as well as by the cytopathologist who interprets the aspirate. If the procedure is done properly, it should have a false-negative rate of less than 5% and a false-positive rate of approximately 1%. [2] Generally, 1 of 4 types of interpretations may be reported, although the nomenclature of classification may vary among institutions: (1) benign, (2) malignant, (3) suspicious for a follicular or Hürthle cell tumor, and (4) insufficient for a diagnosis. If the lesion is either clearly benign or malignant, the management strategy is relatively straightforward. If there is insufficient material for diagnosis, a repeated FNAB should be considered. Insufficient biopsy findings may be owing to poor biopsy technique or cytologic preparations or to the presence of cyst fluid. Even in skilled hands, however, approximately 10% of biopsy findings are nondiagnostic.

A diagnosis of a follicular or Hürthle cell tumor requires further evaluation and management, since the cytologic features of benign follicular or Hürthle cell tumors and low-grade follicular or Hürthle cell cancer are similar. [3] The 2 entities can only be distinguished by the presence or absence of capsular or vascular invasion on histologic examination of surgical specimens. Follicular and Hürthle cell tumors, diagnosed by using FNAB, have a malignancy rate of 10% to 20%.

Blood Tests

Patients with a nodular goiter should have their serum thyrotropin (thyroid-stimulating hormone) concentrations measured in an assay that is sensitive enough to differentiate among euthyroid, hypothyroid (elevated thyrotropin level), and hyperthyroid (suppressed thyrotropin level) states. If the thyrotropin level is elevated, a serum antithyroperoxidase level (formerly called antimicrosomal antibody) may be obtained to confirm Hashimoto thyroiditis, although a neoplasm may coexist as an independent lesion. If the thyrotropin level is suppressed, a measurement of free thyroxine or its estimate should be obtained to document the presence and degree of hyperthyroidism. If the free thyroxine (estimate) is normal and the thyrotropin level is suppressed, a serum total triiodothyronine (T₃) or free T₃ (estimate) may be obtained to rule out "T₃ toxicosis." A suppressed thyrotropin level, with or without an elevation in free thyroxine or free T₃, suggests that the thyroid nodule is benign, but an iodine 123-labeled scan should be performed to confirm the presence of a hyperfunctioning ("hot") nodule, since a hypofunctioning nodule may coexist in the context of underlying hyperthyroidism.

If there is a family history of medullary thyroid cancer (MTC) or MEN II, a basal serum calcitonin level should be obtained, and if it is elevated, MTC is probably present. In such patients, the presence of a pheochromocytoma should also be excluded. If the family history is noncontributory, routine serum

calcitonin measurements are not cost-effective, nor are serum thyroglobulin (Tg) measurements, which do not discriminate between benign and malignant disease.

Imaging of the Thyroid Gland

Radionuclide Scans. Iodine 123 or technetium Tc 99m pertechnetate are useful imaging agents for thyroid nodules, although most specialists who treat patients with thyroid disease prefer iodine 123. While nodules that are hyperfunctioning with iodine 123 and technetium Tc 99m pertechnetate are almost invariably benign, such lesions constitute less than 10% of all nodules. An occasional nodule that is functioning with technetium Tc 99m pertechnetate will be hypofunctioning with iodine 123. Therefore, all nodules that are hot with technetium Tc 99m pertechnetate should be rescanned with iodine 123. Nodules that are either hypofunctioning or eufunctioning with iodine 123 or technetium Tc 99m pertechnetate also are usually benign, but malignancy cannot be excluded. Thus, with the exception of hyperfunctioning nodules, the thyroid scan will not help to differentiate benign from malignant lesions. For this reason, many endocrinologists no longer advocate obtaining thyroid scans as part of the routine initial evaluation of a nodular goiter, and they prefer to perform an FNAB first. However, there are circumstances in which the thyroid scan is useful, including (1) determining if a nodule in a hyperthyroid patient (eg, Graves disease or multinodular goiter) is functioning, since functioning lesions are rarely malignant; (2) determining the functional status of a nodule that has been shown to be a follicular neoplasm by using FNAB; and (3) differentiating the functional status of nodules in a multinodular goiter. In addition, the radionuclide thyroid scan may be helpful when findings on palpation may be difficult to characterize, especially if there is some question about multinodularity, thyroid gland irregularity, or substernal extension.

Ultrasonography. Ultrasonography of the thyroid gland has been commonly used in the initial evaluation of a nodular goiter, but it does not differentiate between benign and malignant lesions. Pure simple cysts are usually benign, but since a vast majority of nodules are solid or have solid components on ultrasonography, the routine use of this procedure generally does not add significant information in easily palpable lesions. It may be useful, however, in selected patients who are undergoing an FNAB (eg, those with complex cysts, those with lesions that are difficult to palpate, or those whose cysts or lesions have been detected fortuitously by using other imaging procedures). Ultrasonography of the thyroid gland also may have utility if there is some question with regard to multinodularity. However, nonpalpable single or multiple nodules (size, <1 cm) that are detected only by using ultrasonography usually have a benign clinical course and generally do not require further evaluation but may be followed with ultrasonography at periodic intervals.

Some clinicians suggest that ultrasound examinations should be obtained in individuals with a history of head or neck irradiation.

Other Imaging Modalities. Other imaging tests (eg, computed tomography or magnetic resonance imaging) have virtually no role in the initial evaluation of the patient with a thyroid nodule. Computed tomography or magnetic resonance imaging may be helpful, however, in determining the extent of a substernal goiter or the presence or degree of tracheal compression.

MANAGEMENT AND FOLLOW-UP OF THE CLINICALLY SOLITARY THYROID NODULE

The Figure outlines a suggested strategy for the evaluation and management of thyroid nodules. An iodine 123-tagged scan may be helpful when a follicular neoplasm has been found on FNAB, since benign hyperfunctioning nodules may be cytologically indistinguishable from nonfunctioning benign follicular neoplasms and follicular cancer.[1] As noted earlier, hyperfunctioning nodules are almost never malignant.

Patients with thyroid nodules in whom malignancy has been excluded or determined to be improbable require long-term periodic clinical observation with judicious use of laboratory tests, imaging procedures,

needle biopsy, and levothyroxine sodium suppression therapy. The goals of follow-up are (1) to recognize progressive enlargement that could result in local compressive complications or cosmetic concerns or may also be signs of malignancy, (2) to diagnose associated clinical or subclinical thyroid dysfunction, and (3) to identify patients in whom there may be an undiagnosed or subsequent thyroid malignant neoplasm.

Periodic assessment should include a history that is focused to identify (1) progressive nodule or goiter enlargement; (2) local compressive and invasive symptoms (ie, dysphagia, dyspnea, cough, pain, hoarseness); (3) other local neck, pulmonary, or skeletal symptoms that would suggest metastatic disease from an undetected thyroid malignant neoplasm; and (4) symptoms that would suggest hyperthyroidism or hypothyroidism, particularly in individuals with functioning adenomas or Hashimoto thyroiditis, respectively.

Follow-up should also include a physical examination that is relevant to the patient's clinical status. The size of the nodule or gland should be quantified and recorded, and evidence of tracheal deviation or regional lymphadenopathy should also be recorded.

The frequency of periodic clinical assessments can and should vary both among patients and over time, from as often as weekly (rarely necessary) to as infrequently as every other year. Factors that govern the frequency of follow-up visits include (1) the degree of diagnostic certainty that the thyroid nodule or goiter is benign, (2) the level of confidence that the nodule or goiter is stable in size, (3) the likelihood of subsequent development of thyroid dysfunction, and (4) the presence of other medical conditions that are potentially complicated by the thyroid disorder.

Typically, relatively few diagnostic tests are needed to manage most patients with thyroid nodules and goiter that are previously thought to be benign. Serial imaging procedures should generally be limited to patients in whom the lesions cannot be readily palpated and in whom the size of the nodule cannot be reliably determined by palpation. In these circumstances, thyroid ultrasonography for lesions that are limited to the neck, and either computed tomography (preferably without contrast) or magnetic resonance imaging for goiters that are located substernally, may be required. Radionuclide scanning is relatively imprecise for the assessment of the size of the nodule or goiter, although there may be a limited role for radionuclide scans to define the function of newly appearing nodules.

Periodic thyroid function testing is necessary in patients with functioning adenomas, multinodular goiters, or coexistent autoimmune thyroiditis. The serum thyrotropin measurement, in an assay with a functional sensitivity of 0.1 mU/L or less, is the most sensitive test to identify individuals with thyroid dysfunction. Periodic serum thyrotropin measurements are also indicated in patients who are treated with levothyroxine. Serial monitoring of serum antithyroid antibody levels is not useful. During the course of follow-up, repeated FNAB may be appropriate to reassess thyroid nodules or goiters under several circumstances as follows: (1) when the lesion continues to enlarge or fails to decrease in size with thyrotropin suppressive therapy; (2) when new clinical features develop that suggest possible malignancy; (3) when the previous cytologic diagnosis was indeterminate, or (4) when there is insufficient material for cytologic diagnosis. Routine repetitive FNAB of lesions that were previously shown to be benign is rarely indicated.

Some patients with benign nodules may benefit from thyrotropin-suppressive therapy with levothyroxine, which may shrink some lesions and prevent progressive enlargement in others.^{[4] [5]} A lack of universal efficacy makes such therapy optional for most patients. Levothyroxine should not be used in individuals with thyrotropin levels that are below normal. Cystic and autonomously functioning (ie, thyrotropin-independent) lesions rarely, if ever, shrink with thyrotropin suppression. Some clinicians use thyrotropin-suppressive therapy in patients with small (eg, <2 cm) follicular neoplasms. If such lesions shrink,

surgery may be avoided. In deciding whether thyroid hormone therapy is appropriate in a given patient, other relevant factors that should be considered are (1) the nodule's pattern of growth or stability, (2) the degree of diagnostic certainty about the nodule's benign character, (3) the patient's potential future perioperative risk and desire to avoid surgery, and (4) the presence of or the risk for the development of other medical conditions that might be exacerbated by thyroid hormone therapy (eg, cardiac disease or osteoporosis).[5] The appropriate duration of thyrotropin-suppressive therapy can vary widely. For some individuals, lifelong thyroid hormone therapy may be justifiable. Regardless of the duration of previous treatment, patients who are taking levothyroxine for thyrotropin suppression should be reevaluated clinically and with a sensitive thyrotropin measurement. Ultrasonography of the thyroid gland may be helpful in determining a change in the size of the nodule, especially with lesions that are difficult to palpate. The potential benefits and risks of therapy should be reassessed at least annually.

MANAGEMENT OF THE CLINICALLY MULTINODULAR, NONTOXIC GOITER

The clinical and laboratory evaluation described and outlined in the Figure for individuals with clinical solitary thyroid nodules is relevant to individuals with a multinodular goiter. The management strategy may differ from individuals with single nodules in the following ways: (1) Thyrotropin-suppressive doses of levothyroxine to treat elderly persons may cause iatrogenic thyrotoxicosis due to areas of autonomy within the goiter and should generally be avoided. (2) Multinodular goiters are more likely than single nodules to result in cosmetic concerns or, if very large, result in pressure symptoms. In such individuals, surgery may be appropriate. (3) Radioactive iodine (ie, iodine 131) has been used successfully to reduce goiter size in selected individuals with a multinodular goiter, in whom surgery is unnecessarily risky or contraindicated.[6] The dose of iodine 131 that is required in such patients is significantly greater than that used for patients with either Graves hyperthyroidism or a toxic nodular goiter.

MANAGEMENT OF THYROID NODULES IN PREGNANCY

A pregnant patient with a thyroid nodule is generally managed like a nonpregnant woman. However, radioisotopes are contraindicated in pregnancy, so radionuclide scans cannot be performed. Thyroid nodules that are clinically suspicious for malignancy can be aspirated during pregnancy. If the results of cytologic studies are positive for malignancy, a decision must be made whether to recommend surgery during the pregnancy or to postpone it until after delivery. Surgery may be performed relatively safely during the second trimester. Since thyroid cancer is generally indolent in its growth, an alternate strategy could be to defer an FNAB until the postpartum period and to use levothyroxine-suppressive therapy in the meantime to inhibit further growth.

THYROID CANCER TREATMENT

The term *differentiated thyroid cancer* encompasses papillary cancer and follicular cancer. Papillary cancer (that includes mixed papillary-follicular cancer) accounts for the majority of thyroid cancers, that is, approximately 75% of cases, whereas follicular cancer accounts for only about 10% of cases. It is important to separate patients with differentiated cancers into those with good to excellent prognoses vs those with poorer prognoses. In general, patients with a low risk for recurrence or death and a good prognosis are those with small tumors (≤ 2 cm), females, and those with neither local invasiveness or distant metastases.[7] Cervical nodal disease as an independent variable may be associated with higher recurrence rates, and bilateral cervical nodal or mediastinal involvement may impart a poorer overall prognosis.[8] Management of such patients is done best by physicians with a particular interest in diseases of the thyroid gland, usually endocrinologists, who are especially knowledgeable about the various modalities of therapy and their appropriate use in individual patients.

PAPILLARY CANCER OF THE THYROID GLAND

Surgery is the primary therapy for patients with papillary thyroid cancer, and it should be performed by a surgeon with expertise in thyroid surgery. The optimal extent of the thyroidectomy is controversial. For single small tumors (< 1.5 cm), most studies do not demonstrate better survival rates after a total thyroidectomy compared with a lobectomy plus an isthmusectomy.[9] However, in many studies,

recurrence rates appear to be higher after a lobectomy vs a total thyroidectomy, even after adjustment for extent of disease.[9] A total thyroidectomy also has the theoretical advantage of permitting total-body radioiodine scanning following surgery to screen for local or distant metastatic spread; also, serum Tg levels will be lower after a total thyroidectomy, allowing this tumor marker to be used more specifically in follow-up. However, the complication rates of a total thyroidectomy are higher, including hypoparathyroidism and injury to the recurrent laryngeal nerves, than after unilateral procedures. This underscores the importance of having surgeons with special expertise perform such operations. A total or near-total thyroidectomy is clearly indicated, when feasible, in patients with locally invasive or distant metastatic disease, as well as in patients with papillary cancer who have a history of head and neck irradiation. A modified radical neck dissection is usually indicated for patients with clinically palpable extensive ipsilateral cervical adenopathy. Radical neck surgery is rarely, if ever, indicated in patients with uncomplicated papillary cancer, but may be indicated when there is locally invasive disease.

RADIOIODINE THERAPY

With regard to radioiodine therapy,[7] therapy with iodine 131 is indicated for most patients with distant metastatic disease. It may also be useful in the therapy for locally invasive neck disease, as well as for some cervical nodal metastases, particularly those that are not amenable to surgery. The routine radioiodine ablation of remnant thyroid tissue in patients with low-risk cancer has not been shown to enhance the survival rate in most studies, and its effect on recurrences is controversial.[8,9] [10] Although many experts recommend ablation of remnant thyroid tissue for almost all patients after a total thyroidectomy, the decision to use radioiodine should be individualized and based on clinical experience. Quantitative radioiodine scanning may be indicated in some patients before therapy with radioactive iodine. If metastatic disease is present, a large dose (generally 100-200 mCi) of iodine 131 is administered. For ablation of remnant thyroid tissue, a dose of 29.9 to 100 mCi of iodine 131 is usually employed. Doses of 30 mCi or greater require hospitalization because of the need for patient isolation, so that outpatient doses of 29.9 mCi are now commonly used, especially for patients with low-risk cancer. Successful ablation is lower with doses of 29.9 mCi compared with higher doses, especially with larger thyroid remnants, but the need for hospitalization is eliminated. Outpatient doses of 29.9 mCi may be repeated, however. Thus, no firm recommendation can be made with regard to the optimal radioiodine dose.

Prior to radioiodine body scanning and therapy, levothyroxine must be withheld or withdrawn for approximately 4 to 6 weeks to maximize thyrotropin stimulation of the remaining thyroid tissue. The resulting hypothyroidism is tolerated poorly by some patients, and it may be attenuated by the administration of liothyronine sodium, for the first 3 to 4 weeks after levothyroxine therapy is discontinued, ensuring a shorter duration of hypothyroidism. Approximately 2 weeks after treatment with liothyronine is withdrawn, a serum thyrotropin level is obtained to confirm hypothyroidism; a thyrotropin value of greater than 30 mU/L prior to radioiodine therapy is optimal for scanning and therapy. Some clinicians recommend a low-iodine diet for at least 2 weeks prior to radioiodine administration. Pregnancy must be excluded in women of childbearing age prior to radioiodine administration.

LEVOTHYROXINE THERAPY

Most clinicians favor thyrotropin suppressive therapy with levothyroxine for patients with papillary cancer, although the benefit of such suppression has not been clearly documented in patients with low-risk tumors. Cancer recurrence and the mortality rate may be higher in patients who are inadequately treated with levothyroxine, possibly because of thyrotropin stimulation of thyroid cancer cell growth.[11] If thyrotropin suppressive therapy is used, it is not currently certain to what level the serum thyrotropin must be suppressed to maximize the benefit of therapy, while avoiding long-term potential complications of excessive levothyroxine administration (eg, increased bone loss [particularly in postmenopausal women], cardiac hypertrophy, or cardiac arrhythmias).[12] [13] In patients with low-risk tumors, it may be reasonable to give levothyroxine in doses that maintain thyrotropin at or just below the lower limits of

normal. In patients with higher-risk tumors, however, more aggressive therapy to produce thyrotropin levels that are undetectable in third-generation thyrotropin assays is recommended by some experts, although the benefit of such therapy and how long to maintain thyrotropin suppression has not been established.

SERUM Tg

Thyroglobulin is a large protein that is synthesized only by thyroid tissue, including normal thyroid cells, benign thyroid nodules, and well-differentiated thyroid cancers. In the absence of normal thyroid tissue, it is a sensitive and specific marker for the presence of thyroid cancer, since Tg levels should be virtually undetectable after a total thyroidectomy and radioiodine ablation.[\[14\]](#) It is important to use a reliable Tg assay, and to screen for the presence of interfering antithyroglobulin antibodies that may give falsely high or low Tg results; reliable clinical laboratories screen for such antibodies. The release of Tg from thyroid cells is, in part, thyrotropin-dependent. Therefore, a low Tg value while patients are receiving thyrotropin suppressive therapy may be misleadingly reassuring.[\[15\]](#) Thyroglobulin is most sensitive and specific as a tumor marker in the patient who has no remnant of thyroid tissue and who has an elevated thyrotropin level, as occurs in preparation for a radioiodine scan; a low Tg value in this setting is evidence against residual or recurrent disease, and some experts believe such a finding may obviate the need for further radioiodine scanning. Conversely, a normal or elevated Tg concentration in a patient who has undergone previous ablation strongly suggests residual or recurrent disease, whether or not the patient is taking a thyroid hormone.

FOLLICULAR CANCER OF THE THYROID GLAND

Follicular cancers are classified into minimally invasive and (extensively) invasive categories. Patients with minimally invasive follicular cancer have an excellent prognosis. The presence of capsular invasion or, at most, a few areas of blood vessel invasion distinguishes minimally invasive follicular cancer from a benign cellular follicular adenoma. In contrast, patients with follicular cancer with extensive vascular invasion have a poorer prognosis; distant metastases in lung or bones are sometimes present at the time of diagnosis.

Almost all endocrinologists agree that therapy for patients with invasive follicular cancer should consist of a total or near-total thyroidectomy, usually followed by a radioactive iodine ablation of remnant thyroid tissue.[\[16\]](#) Lifelong thyrotropin suppression may be indicated for such patients, by using Tg and periodic radioiodine scans (where indicated) to monitor for recurrence.

The optimal therapy for minimally invasive follicular cancer is more controversial. Some endocrinologists recommend postoperative radioactive iodine scanning and ablation therapy (when appropriate), followed by thyrotropin suppressive therapy. Minimally invasive follicular cancer is often indistinguishable from benign follicular neoplasms at the time of surgery, even by frozen section; a definitive diagnosis often requires multiple sections through the primary tumor. When a lobectomy alone has been performed and minimally invasive follicular cancer is diagnosed after a histologic examination has been completed, 3 alternative therapies may be considered: (1) levothyroxine suppressive therapy alone, (2) completion thyroidectomy followed by radioactive iodine scanning, and (3) radioiodine ablation of the remaining lobe with subsequent radioactive iodine scanning.

FOLLOW-UP OF PATIENTS WITH PAPILLARY OR FOLLICULAR CANCER OF THE THYROID GLAND

The follow-up of patients with papillary or follicular cancer should be appropriate for the stage and extent of the disease. Occult foci (nonpalpable lesions, <1 cm) of papillary cancer that are discovered at the time of a lobectomy for benign thyroid disease may not require additional therapy or testing. Most endocrinologists agree that suppression of thyrotropin is appropriate for all patients with clinically important well-differentiated thyroid cancer. The degree of suppression should be individualized to avoid complications of subclinical hyperthyroidism. Serum Tg levels should be followed up in all patients.

Many endocrinologists suggest that Tg and sensitive thyrotropin measurements should be obtained every 6 months for the first 3 years after initial therapy, and then yearly thereafter.

Some clinicians withdraw thyroid hormone therapy annually for 1 to 3 years for radioactive iodine scanning, especially for patients with high-risk cancer.^[7] If residual or recurrent disease is detected, radioiodine therapy is administered. Other investigators withdraw thyroid hormone annually for the purpose of measuring Tg levels, and determine the need for a scan based on the Tg result. Most endocrinologists individualize the frequency of repeated radioiodine scans, and do repetitive scanning only for those patients with aggressive disease or elevated or rising serum Tg levels. The anticipated availability of recombinant human thyrotropin to stimulate both radioactive iodine uptake for scanning and Tg measurements may alter these practice patterns. Chest radiographs may be obtained periodically, with the frequency dependent on the individual clinical situation. Bone pain should be evaluated initially with appropriate radiographs, since bone scans may be normal despite bony metastases. Some endocrinologists obtain periodic neck ultrasound examinations, particularly in patients with previous locally invasive disease and in patients who have had a lobectomy as their only surgical procedure, because radioiodine scanning is not possible. In patients with elevated or rising Tg levels and normal radioiodine scans, repeated scanning may be indicated after a therapeutic dose of radioiodine. If scans are normal and the serum Tg level is high, ultrasonography of the neck, as well as appropriate computed tomography scans or magnetic resonance imaging, may be indicated. Evaluation of the skeleton and central nervous system is particularly important, to avoid the consequences of undetected brain or spinal cord metastases. Other scanning agents (eg, thallium 201 or sestamibi) may be useful to search for occult metastases in selected patients.

ADDITIONAL THERAPIES

Thyroidectomy, radioactive iodine, and levothyroxine suppressive therapy are sufficient for most patients with well-differentiated thyroid cancer. Locally recurrent disease should be resected if at all possible. When resection is not feasible, external radiation may be helpful in controlling local tumor growth, including but not limited to the neck, mediastinum, bone, spinal cord, and brain.^[17] When a large mass of unresectable tumor is present and the uptake of radioiodine is limited, or when there is intractable bone pain, external beam radiation should be considered. Chemotherapy is of limited efficacy, but it may be considered in patients with symptomatic or relentlessly advancing disease.

SPECIAL CONSIDERATIONS

MEDULLARY THYROID CANCER

Medullary thyroid cancer has unique clinical implications.^[18] Since MTC may be familial, a comprehensive approach to the patient and the family is required. Even if there is no family history of MTC, it is impossible to rule out the possibility that the patient represents the index case of a kindred with MTC. Therefore, if there is a preoperative diagnosis of MTC, usually after a biopsy of the thyroid nodule or enlarged lymph node is performed, it is important to perform appropriate preoperative biochemical testing for pheochromocytomas (usually bilateral) and, if detected, to resect them prior to thyroid surgery. A total thyroidectomy and central neck dissection must be performed for treatment of MTC, with every effort to remove all possible disease by sufficient systematic node dissection. Postoperative basal calcitonin levels provide evidence for the adequacy of resection and are used to test for residual disease or recurrence. In addition, carcinoembryonic antigen is another tumor marker that is often elevated in patients with MTC.

The best available treatment of persistent or recurrent disease is surgical resection, when possible. Progressive unresectable disease may be treated with external beam radiotherapy; however, this has not been shown to improve the survival rate. Chemotherapy is usually ineffective. Fortunately, some patients may survive for many years with minimal symptoms despite significant tumor burdens. Patients with considerable unresectable disease may have chronic diarrhea, which should be treated symptomatically.

Nutmeg oil, a combination of atropine sulfate and diphenoxylate hydrochloride (Lomotil), or subcutaneously administered somatostatin analogue have been effective in such cases.

Approximately 25% of MTCs are familial, usually in the context of MEN IIa or IIb or familial (non-MEN) MTC. It is therefore essential to obtain a detailed family history. Individuals with MEN IIb (MTC, pheochromocytoma) have a phenotype that is also characterized by mucosal neuromas, so they should be distinguishable from patients with MEN IIa (MTC, pheochromocytoma, and hyperparathyroidism). Most patients with MEN IIb and MTC are curable only if a thyroidectomy is performed before clinical disease is apparent. Genetic testing to identify mutations in the *RET* proto-oncogene of patients with familial MTC has become clinically available, and this type of testing is very useful in identifying affected individuals. In addition, since familial MTC is expressed as an autosomal dominant trait, all first-degree relatives of patients with familial MTC must be screened. Traditionally, it has been standard practice to obtain basal and pentagastrin-stimulated serum calcitonin levels for this purpose, but genetic testing for the presence of *RET* proto-oncogene mutations may well replace the cumbersome, repetitive, and expensive stimulation tests with multiple calcitonin determinations. The role of surgery based on abnormal results of DNA tests in family members is currently being investigated. Patients who are identified with familial MTC by using DNA testing or serum calcitonin elevations should undergo a prophylactic total thyroidectomy. Recent trends are to perform a total thyroidectomy on children with positive *RET* mutations between 5 and 7 years of age.^[19] Periodic biochemical screening for pheochromocytomas must be done indefinitely. Likewise, patients with MEN IIa must undergo screening for hyperparathyroidism.

UNDIFFERENTIATED (ANAPLASTIC) THYROID CANCER

Anaplastic thyroid cancer is the most aggressive and lethal solid tumor that occurs in humans; fortunately, it is the least common form of thyroid cancer.^[20] With rare exception, it is rapidly fatal, usually within months of the diagnosis. Anaplastic cancer usually does not concentrate iodine or express Tg, so radioiodine scanning or therapy is of no utility and serum Tg measurements cannot be used as reliable tumor markers. It is essential to verify the diagnosis histologically since insular cancer, lymphomas, and MTCs that require different therapeutic approaches are occasionally confused with undifferentiated cancers.

Surgical treatment is of very limited usefulness and is indicated primarily for relief of airway obstruction. External-beam radiotherapy has been helpful in delaying local recurrence and preventing thoracic outlet obstruction, especially after surgery has been performed. However, this treatment has not been shown to alter the mortality rate. Chemotherapy has not been found to be effective for this tumor despite a variety of approaches that utilize single agents or various combinations of doxorubicin hydrochloride, etoposide (VP-16), cisplatin, and bleomycin sulfate. Rarely, partial responses to chemotherapy can prolong survival by several months. The role of chemotherapy, followed by external radiation and surgery, while also rarely if ever curative, has been reported to extend survival, in some patients; such an approach may need to be evaluated further. The most practical patient care requires close attention to pain control, maintenance of the airway, and other quality-of-life issues.

Occasionally, previously well-differentiated papillary or follicular thyroid cancer undergoes anaplastic dedifferentiation, and patients with such conditions should be managed as just described. On the other hand, some tumors are in intermediate states of dedifferentiation, in which tumor growth may be slower. When this occurs, resectable tumor should be removed, and external radiotherapy, and perhaps chemotherapy, should be used for unresectable or incompletely resectable metastases. Suppression of thyrotropin with levothyroxine therapy has not been proved to be beneficial, but replacement therapy is indicated.

LYMPHOMA OF THE THYROID GLAND

Primary non-Hodgkin lymphoma of the thyroid gland, an uncommon thyroid tumor, must be considered in the context of a rapidly growing goiter, particularly in older women with hypothyroidism because of autoimmune (Hashimoto) thyroiditis.^[21] The FNAB is the initial diagnostic procedure of choice that is sometimes aided by B-cell immunotyping with flow cytometry, but open biopsy for pathologic confirmation is often required for a definitive diagnosis. Since this tumor requires a unique therapeutic approach, it must be distinguished from anaplastic and MTC, since there appears to be little benefit of surgical therapy for lymphomas. After diagnosis, patients can be clinically staged (without surgery) through use of appropriate computed tomography scans and magnetic resonance imaging. They are designated stage IE with disease confined to the thyroid gland (with possible local invasion), stage IIE with local lymph node metastases, stage IIIE with distant nodal metastases, or stage IV with diffuse involvement of multiple organs and sites.

Since distant metastases may develop in almost one third of patients with stage IE and IIE disease, and many patients present with micrometastatic disease, recent studies have demonstrated the best success with combined therapy, by using systemic chemotherapy and external radiotherapy to the neck and mediastinum. Although a variety of chemotherapeutic regimens have been used, most successful treatments have included an anthracycline agent.

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