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Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Taskforce*

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Thyroid Cancer Guidelines

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Introduction

THYROID NODULES are a common clinical problem. Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world (1,2). In contrast, high-resolution ultrasound can detect thyroid nodules in 19%–67% of randomly selected individuals with higher frequencies in women and the elderly (3). The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer that occurs in 5%–10% depending on age, gender, radiation exposure history, family history, and other factors (4, 5). Differentiated thyroid cancer, which includes papillary and follicular cancer, comprises the vast majority (90%) of all thyroid cancers (6). In the United States, approximately 23,500 cases of differentiated thyroid cancer are diagnosed each year (7), and the yearly incidence may be increasing (8).

In 1996, the American Thyroid Association (ATA) published treatment guidelines for patients with thyroid nodules and thyroid cancer (9). Over the last decade, there have been many advances in the diagnosis and therapy of both thyroid nodules and differentiated thyroid cancer. Controversy exists in many areas, including the most cost-effective approach in the diagnostic evaluation of a thyroid nodule, the extent of surgery for small thyroid cancers, the use of radioactive iodine to ablate remnant tissue after thyroidectomy, the appropriate use of thyroxine suppression therapy, and the role of human recombinant thyrotropin. In recognition of the changes that have taken place in the overall management of these clinically important problems, the ATA appointed a task force to reexamine the current strategies that are used to diagnose and treat thyroid nodules and differentiated thyroid cancer, and to develop clinical guidelines using principles of evidence-based medicine. Members of the taskforce included experts in thyroid nodule and thyroid cancer management with representation by endocrinology, surgery, and nuclear medicine. Other groups have previously developed guidelines, including the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons (10), the British Thyroid Association and The Royal College of Physicians (11), and the National Comprehensive Cancer Network (12), which have provided somewhat conflicting recommendations because of the lack of high-quality evidence from randomized controlled trials.

Materials and Methods

The ATA guidelines taskforce used a strategy similar to that used by the National Institutes of Health for its Consensus Development Conferences (www.consensus.nih.gov/about/process.htm), and developed a series of clinically relevant questions pertaining to thyroid nodule and thyroid cancer diagnosis and treatment. These questions were as follows:

Thyroid Nodules

- What is the appropriate evaluation of clinically or incidentally discovered thyroid nodule(s)?
  - What laboratory tests and imaging modalities are indicated?
  - What is the role of fine needle aspiration (FNA)?
- What is the best method of long-term follow-up of patients with thyroid nodules?
- What is the role of medical therapy of patients with benign thyroid nodules?
- How should thyroid nodules in children and pregnant women be managed?

Differentiated Thyroid Cancer: Initial Management

- What is the role of preoperative staging with diagnostic imaging and laboratory tests?
- What is the appropriate operation for differentiated thyroid cancer?
- What is the role of postoperative staging systems and which should be used?
- What is the role of postoperative radioiodine remnant ablation?
- What is the role of thyrotropin suppression therapy?
- Is there a role for adjunctive external beam irradiation or chemotherapy?

Differentiated Thyroid Cancer: Long-Term Management

- What are the appropriate features of long-term management?
- What is the role of serum thyroglobulin assays?
- What is the role of ultrasound and other imaging techniques during follow-up?
- What is the role of thyrotropin suppression in long-term follow-up?
- What is the most appropriate management of patients with metastatic disease?
- How should thyroglobulin positive, scan negative patients be managed?
- What is the role of external radiation therapy
- What is the role of chemotherapy?
- What are directions for future research?

A 2-day meeting of the taskforce was held on January 21–23, 2005. Prior to the meeting, the taskforce members undertook a complete literature review. Relevant articles were identified by searching MEDLINE using the following search terms: {THRYOID NODULE/diagnosis, drug therapy, surgery, therapy, ultrasonography} or {CANCER} or {CARCINOMA} and {THYROID} and {FOLLICULAR CARCINOMA} or {PAPILLARY CACINOMA} and {FOLLOW-UP} and {TREATMENT} and {RECURRENCE}. All English-language papers published between 1995 and December 2004 were reviewed and categorized in tabular form by date, author, subject, and whether it represented a randomized controlled trial, meta-analysis, or clinical case series. Relevant review articles, book chapters, and pre-1995 articles were also supplied by taskforce members. The taskforce categorized the published data using modified criteria adopted from the U.S. Preventive Services Task Force (USPSTF) (13). The taskforce then made specific recommendations, rated the strength of the recommendation using the schema proposed by the USPSTF (Table 1). Given the paucity of randomized controlled trials in the treatment of thyroid cancer, the panel relied on all the available published evidence. When evidence was judged to be insufficient, the taskforce members also relied on their experience and judgment to answer the

questions that had been posed. The taskforce met again in April 2005 and in June 2005 to refine the document and include new references. Supplementing these meetings were multiple teleconferences and detailed e-mail communications that continued through July 2005.

Results

Thyroid nodules

A thyroid nodule is a discrete lesion within the thyroid gland that is palpably and/or ultrasonographically distinct from the surrounding thyroid parenchyma. However, some palpable lesions may not correspond to distinct radiologic abnormalities (14). Such abnormalities do not meet the strict definition for thyroid nodules. Other nonpalpable nodules are easily seen on ultrasound or other anatomic imaging studies, and are termed incidentally discovered nodules or "incidentalomas." Nonpalpable nodules have the same risk of malignancy as palpable nodules with the same size (15). Generally, only nodules larger than 1 cm should be evaluated, because they have the potential to be clinically significant cancers. Occasionally, there may be nodules smaller than 1 cm that require evaluation, because of suspicious ultrasound findings, a history of head and neck irradiation, or a positive family history of thyroid cancer.

What is the appropriate evaluation of clinically or incidentally discovered thyroid nodule(s)?

With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed (Fig. 1). Pertinent historical factors predicting malignancy include a history of head and neck irradiation, total body irradiation for bone marrow transplantation (16), family history of thyroid carcinoma in a first-degree relative, exposure to fallout from Chernobyl under the age of 14 years (17), and rapid growth and hoarseness. Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, ipsilateral cervical lymphadenopathy and fixation of the nodule to surrounding tissues.

What laboratory tests and imaging modalities are indicated?

Serum thyrotropin and imaging studies. With the discovery of a thyroid nodule larger than 1–1.5 cm in any diameter, a serum thyrotropin (TSH) level should be obtained. If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is functioning (i.e., has tracer uptake greater than the surrounding normal thyroid), isofunctioning or "warm" (i.e., has tracer uptake equal to the surrounding thyroid), or nonfunctioning (i.e., has uptake less than the surrounding thyroid tissue). Because functioning nodules rarely harbor malignancy, if one is found that corresponds to the clinical nodule, no additional cytologic evaluation is necessary. If overt or subclinical hyperthyroidism is present, additional evaluation is required.

R1. Measure serum TSH in the initial evaluation of a patient with a thyroid nodule—Recommendation C

Diagnostic thyroid ultrasound should be performed unless the serum TSH is suppressed. Thyroid ultrasound can

TABLE 1. STRENGTH OF PANELISTS' RECOMMENDATIONS BASED ON AVAILABLE EVIDENCE

Rating	*Definition*
A	**Strongly recommends.** The recommendation is based on good evidence that the service or intervention can improve important health outcomes. Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
B	**Recommends.** The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.
C	**Recommends.** The recommendation is based on expert opinion.
D	**Recommends against.** The recommendation is based on expert opinion.
E	**Recommends against.** The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
F	**Strongly recommends against.** The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
I	**Recommends neither for nor against.** The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.

Source: Adapted from the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality.

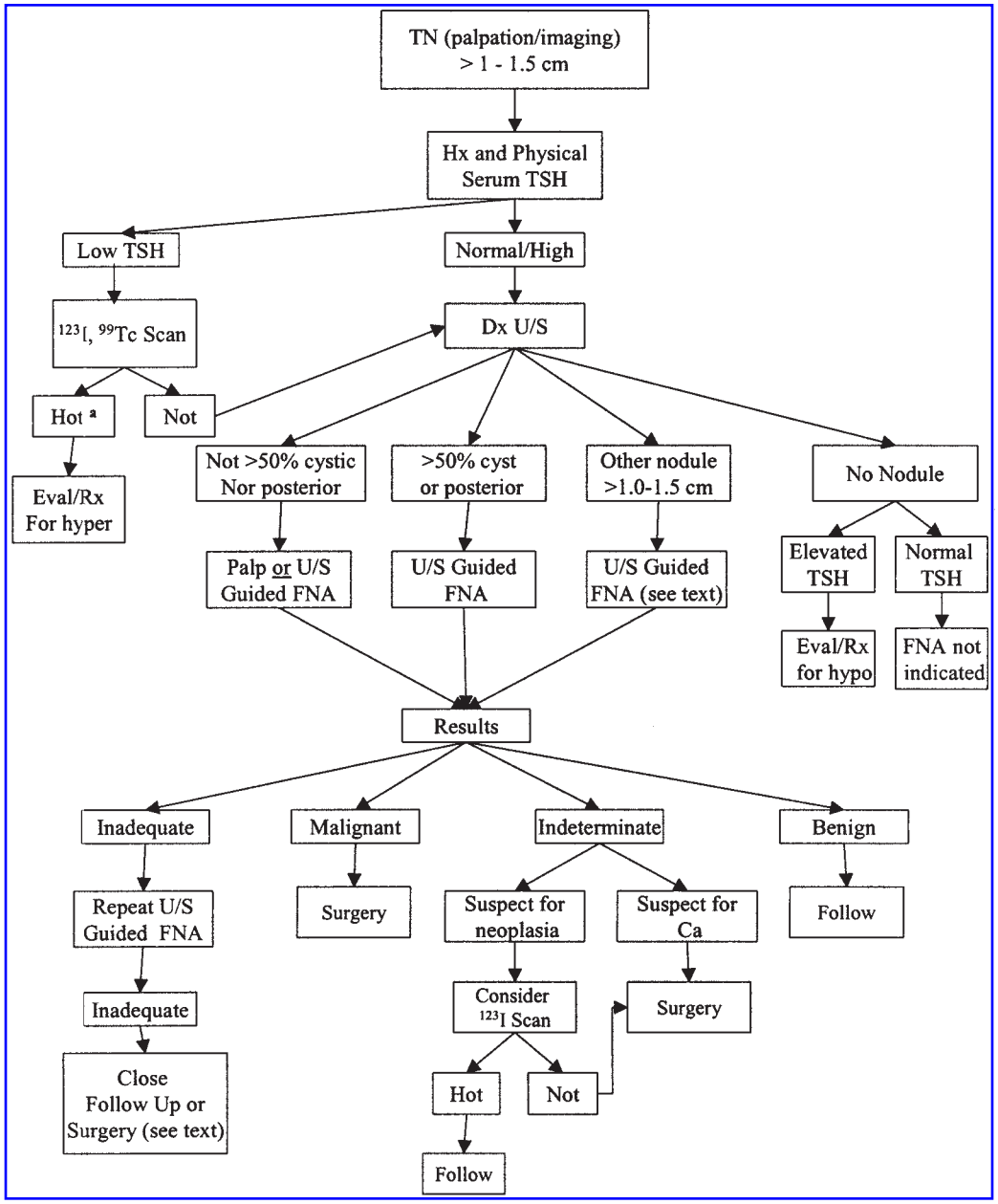

FIG. 1. Algorithm for the evaluation of patients with one or more thyroid nodules. [a]If the scan does not show uniform distribution of tracer activity, ultrasound may be considered to assess for the presence of a cystic component

answer the following questions: Is there truly a nodule that corresponds to the palpable abnormality? Is the nodule greater than 50% cystic? Is the nodule located posteriorly in the thyroid gland? These last two features might decrease the accuracy of fine needle aspiration biopsy performed with palpation (18,19). Also, there may be other thyroid nodules present that require biopsy based on their size and appearance (14,20,21). Even if the TSH is elevated, FNA is recommended because the rate of malignancy in nodules is similar in thyroid glands involved with Hashimoto's thyroiditis as in normal thyroid glands (22).

R2. Thyroid sonography should be performed in all patients with one or more suspected thyroid nodules—Recommendation B

Other laboratory testing:

Serum thyroglobulin measurement. Serum thyroglobulin levels can be elevated in most thyroid diseases and is an insensitive and nonspecific test for thyroid cancer (23).

R3. Routine measurement of serum thyroglobulin for initial evaluation of thyroid nodules is not recommended—Recommendation F

Serum calcitonin measurement. The utility of serum calcitonin has been evaluated in a series of prospective, nonrandomized studies (24–26). The data suggest that the use of routine serum calcitonin for screening may detect C-cell hyperplasia and medullary thyroid cancer at an earlier stage

and overall survival may be improved. However, there remain unresolved issues of sensitivity, specificity, assay performance, and cost effectiveness. Furthermore, most studies rely on pentagastrin stimulation testing to increase specificity and this drug is no longer available in the United States. However, if the unstimulated serum calcitonin determination has been obtained and the level is greater than 100 pg/mL, medullary cancer is likely present (27).

R4. The panel cannot recommend either for or against the routine measurement of serum calcitonin—Recommendation I

What is the role of FNA biopsy?

FNA is the most accurate and cost effective method for evaluating thyroid nodules. Traditionally FNA biopsy results are divided into four categories: nondiagnostic, malignant, indeterminate or suspicious for neoplasm, and benign. Nondiagnostic biopsies are those that fail to meet specified criteria for adequacy that have been previously established (5). Such biopsies need to be repeated using ultrasound guidance (28). Some nodules, particularly those that are cystic, continue to yield nondiagnostic cytology results despite repeated biopsies, and may be malignant at the time of surgery (29,30).

R5. FNA is the procedure of choice in the evaluation of thyroid nodules—Recommendation A

Nondiagnostic aspirates

R6. Cystic nodules that repeatedly yield nondiagnostic aspirates need close observation or surgical excision. Surgery should be more strongly considered if the cytologically nondiagnostic nodule is solid—Recommendation A

Aspirates suggesting malignancy

R7. If a cytology result is diagnostic of malignancy, surgery is recommended (31)—Recommendation A

Indeterminate cytology

Indeterminate cytology, often reported as "suspicious," "follicular lesion," or "follicular neoplasm," can often be found in 15%–30% of FNA specimens. While certain clinical features such as gender and nodule size (32) or cytologic features such as presence of atypia (33) can improve the diagnostic accuracy in patients with indeterminate cytology, overall predictive values are still low. Many molecular markers have been evaluated to improve diagnostic accuracy for indeterminate nodules (34,35) but none can be recommended because of insufficient data.

R8. At the present time, the use of specific molecular markers to improve the diagnostic accuracy of indeterminate nodules is not recommended—Recommendation I

R9. If the cytology reading is indeterminate (often termed "suspicious," "follicular lesion," or "follicular neoplasm"), a radioiodine thyroid scan should be considered, if not already done. If a concordant autonomously functioning nodule is not seen, lobectomy or total thyroidectomy should be considered—Recommendation B

R10. If the reading is "suspicious for papillary carcinoma or Hürthle cell neoplasm," a radionuclide scan is not needed, and either lobectomy or total thyroidectomy is recommended—Recommendation A (36)

Benign cytology

R11. If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not routinely required—Recommendation A

Multinodular goiters

Patients with multiple thyroid nodules have the same risk of malignancy as those with solitary nodules (14,37). A diagnostic ultrasound should be performed to delineate the nodules, but if only the "dominant" or largest nodule is aspirated, the thyroid cancer may be missed (14). Sonographic characteristics are superior to nodule size for identifying nodules that are more likely to be malignant (37,38) and include the presence of microcalcifications, hypoechogenicity (darker than the surrounding thyroid parenchyma) of a solid nodule, and intranodular hypervascularity (37,38). The detection of microcalcifications and nodular vascularity has good interobserver reliability (39).

R12a. In the presence of two or more thyroid nodules larger than 1–1.5 cm, those with a suspicious sonographic appearance should be aspirated preferentially—Recommendation B

R12b. If none of the nodules has a suspicious sonographic appearance and multiple sonographically similar coalescent nodules are present, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodules only—Recommendation C

R13. A low or low-normal serum TSH concentration may suggest the presence of autonomous nodule(s). A radioiodine scan should be performed and directly compared to the ultrasound images to determine functionality of each nodule larger than 1–1.5 cm. FNA should then be considered only for those isofunctioning or nonfunctioning nodules, among which those with suspicious sonographic features should be aspirated preferentially—Recommendation B

What is the best method of long-term follow-up of patients with thyroid nodules?

Thyroid nodules diagnosed as benign require follow-up because of a low, but not negligible, false-negative rate of up to 5% with FNA (40,41). While benign nodules may decrease in size, they often increase in size, albeit slowly (42). Nodule growth is not in and of itself an indication of malignancy, but growth is an indication for repeat biopsy. For nodules with benign cytologic results, recent series report a higher false negative rate with palpation FNA (1%–3%) (43–45) than with ultrasound FNA (0.6%) (44). In one study investigating the value of routine reaspirations of benign nodules, the nodule grew in the three patients who were subsequently found to have thyroid cancer (37). Because the accuracy of physical examination for nodule size is likely inferior to that of ultrasound (21), it is recommended that serial ultrasound be used in follow-up of thyroid nodules to detect clinically sig-

nificant changes in size. There is no consensus on the definition of nodule growth, however, or the threshold that would require rebiopsy. Some groups suggest a 15% increase in nodule volume, while others recommend measuring a change in the mean nodule diameter (42,46). One reasonable definition of growth is a 20% increase in nodule diameter with a minimum increase in two or more dimensions of at least 2 mm. The false-negative rate for benign thyroid nodules on repeat FNA is low (47).

R14. Easily palpable benign nodules do not require sonographic monitoring, but patients should be followed clinically at 6–18 month intervals. It is recommended that all other benign thyroid nodules be followed with serial ultrasound examinations 6–18 months after initial FNA. If nodule size is stable, the interval before the next follow-up clinical examination or ultrasound may be longer—Recommendation B

R15. If there is evidence for nodule growth either by palpation or sonographically, repeat FNA, preferably with ultrasound guidance—Recommendation B

What is the role of medical therapy for benign thyroid nodules?

Evidence from multiple randomized control trials and three metaanalyses suggest that thyroid hormone in doses that suppress the serum TSH to subnormal levels may result in a decrease in nodule size in regions of the world with borderline low iodine intake. Data in iodine sufficient populations are less compelling (48–50).

R16. The panel does not recommend routine suppression therapy of benign thyroid nodules—Recommendation F

R17. Patients with growing nodules that are benign after repeat biopsy should be considered for continued monitoring or intervention with surgery based on symptoms and clinical concern—Recommendation C. There are no data on the use of levothyroxine in this subpopulation of patients—Recommendation I

How should thyroid nodules in children and pregnant women be managed?

Thyroid nodules in children. Thyroid nodules occur less frequently in children than in adults. In one study in which approximately 5000 children aged 11 to 18 were assessed annually in the southwestern United States, palpable thyroid nodules occurred in approximately 20 per 1000 children, with an annual incidence of 7 new cases per 1000 children (51). Some studies have shown the frequency of malignancy to be higher in children than adults, in the 15%–20% range (52–54), whereas other data have suggested that the frequency of thyroid cancer in childhood thyroid nodules is similar to that of adults (55,56). FNA biopsy is sensitive and specific in the diagnosis of childhood thyroid nodules (53–55).

R18. The diagnostic and therapeutic approach to one or more thyroid nodules in a child should be the same as it would be in an adult (clinical evaluation, serum TSH, ultrasound, FNA)—Recommendation A

Thyroid nodules in pregnant women. It is uncertain if thyroid nodules discovered in pregnant women are more likely to be malignant than those found in nonpregnant women (57), because there are no population-based studies on this question. The evaluation is the same as for a nonpregnant patient, with the exception that a radionuclide scan is contraindicated.

R19. For euthyroid and hypothyroid pregnant women with thyroid nodules, FNA should be performed. For women with suppressed serum TSH levels that persist after the first trimester, FNA may be deferred until after pregnancy when a radionuclide scan can be performed to evaluate nodule function—Recommendation A

If the FNA cytology is consistent with thyroid cancer, surgery is recommended. However, there is no consensus about whether surgery should be performed during pregnancy or after delivery. To minimize the risk of miscarriage, surgery during pregnancy should be done before 24 weeks' gestation (58). However, thyroid cancer discovered during pregnancy does not behave more aggressively than that diagnosed in a similar aged group of nonpregnant women (59,60). A retrospective study of pregnant women with differentiated thyroid cancer found there to be no difference in either recurrence or survival rates between women operated on during or after their pregnancy (60). Furthermore, retrospective data suggest that treatment delays of less than 1 year from the time of thyroid cancer discovery do not adversely effect patient outcome (61).

R20. A nodule with malignant cytology discovered early in pregnancy should be monitored sonographically and if it grows substantially (as defined above) by 24 weeks' gestation, surgery should be performed at that point. However, if it remains stable by midgestation or if it is diagnosed in the second half of pregnancy, surgery may be performed after delivery—Recommendation C

Differentiated Thyroid Cancer: Initial Management

Goals of initial therapy of differentiated thyroid cancer are:

1. *To remove the primary tumor, disease that has extended beyond the thyroid capsule, and involved cervical lymph nodes*. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease recurrence (62–64).
2. *To minimize treatment- and disease-related morbidity*. The extent of surgery and the experience of the surgeon both play important roles in determining the risk of surgical complications (65,66).
3. *To permit accurate staging of the disease*. Because disease stage can assist with prognostication, disease management and follow-up strategies, accurate postoperative staging is a crucial element in the management of patients with differentiated thyroid cancer (67,68).
4. *To facilitate postoperative treatment with radioactive iodine, where appropriate*. For patients undergoing radioiodine remnant ablation, or radioiodine treatment of residual or

metastatic disease, removal of all normal thyroid tissue is an important element of initial surgery (69). Near-total or total thyroidectomy also may reduce the risk for recurrence within the contralateral lobe (70).

5. *To permit accurate long-term surveillance for disease recurrence*. Both radioiodine whole-body scanning and measurement of serum thyroglobulin are affected by residual normal thyroid tissue. Where these approaches are utilized for long-term monitoring, near-total or total thyroidectomy is required (71).
6. *To minimize the risk of disease recurrence and metastatic spread*. Adequate surgery is the most important treatment variable influencing prognosis, while radioactive iodine treatment, thyrotropin suppression and external beam irradiation each play adjunctive roles in at least some patients (71–74).

What is the role of preoperative staging with diagnostic imaging and laboratory tests?

Neck imaging. Differentiated thyroid carcinoma (particularly papillary carcinoma) involves cervical lymph nodes in 20%–50% of patients in most series using standard pathologic techniques (75–79), and may be present even when the primary tumor is small and intrathyroidal (37,80). The frequency of micrometastases may approach 90%, depending on the sensitivity of the detection method (81,82). Preoperative ultrasound identifies suspicious cervical adenopathy in 20%–31% of cases, potentially altering the surgical approach (83,84), although prospective studies are needed.

Accurate staging is important in determining the prognosis and tailoring treatment for patients with differentiated thyroid cancer. However, unlike many tumor types, the presence of metastatic disease does not obviate the need for surgical excision of the primary tumor in differentiated thyroid cancer (85). Because metastatic disease may respond to radioiodine therapy, removal of the thyroid as well as the primary tumor and accessible loco-regional disease remains an important component of initial treatment even in metastatic disease.

As ultrasound evaluation is uniquely operator dependent, alternative imaging procedures may be preferable in some clinical settings, though the sensitivity of computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scan remain unknown in this setting. These alternative imaging modalities, as well as laryngoscopy and endoscopy, may also be useful in the assessment of large, rapidly growing, or invasive tumors, to assess the involvement of extrathyroidal tissues (86,87).

R21. Preoperative neck ultrasound for the contralateral lobe and cervical (central and bilateral) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant cytologic findings on biopsy—Recommendation B

R22. Routine preoperative use of other imaging studies (CT, MRI, PET) is not recommended—Recommendation E

Measurement of serum thyroglobulin. There is some evidence that high preoperative concentrations of serum thyroglobulin may predict a higher sensitivity for post-operative surveillance with serum thyroglobulin (88). Evidence that this impacts patient management or outcomes is not yet available.

R23. Routine preoperative measurement of serum thyroglobulin is not currently recommended—Recommendation E

What is the appropriate operation for differentiated thyroid cancer?

Surgical options for indeterminate biopsies or biopsies diagnostic of differentiated thyroid carcinoma. The goal of thyroid surgery can include provision of a diagnosis after a nondiagnostic or indeterminate biopsy, removal of the thyroid cancer, staging, and preparation for radioactive ablation. Surgical options for thyroid cancer should be limited to lobectomy, near-total thyroidectomy (removal of all grossly visible thyroid tissue, leaving only a small amount (< 1 gram) of tissue adjacent to the insertion of the recurrent laryngeal nerve into the cricothyroid muscle), and total thyroidectomy (removal of all grossly visible thyroid tissue). Subtotal thyroidectomy, leaving more than 1 gram of tissue with the posterior capsule on the involved side, is an inappropriate operation for thyroid cancer (89).

Surgery for a nondiagnostic biopsy, a biopsy suspicious for papillary cancer, a biopsy suggestive of "follicular neoplasm," including special consideration for patients with other risk factors. Among solitary thyroid nodules with an indeterminate ("suspicious," "follicular neoplasm," or Hürthle cell neoplasm) biopsy, the risk of malignancy is approximately 20% (90–92). For solitary nodules that are repeatedly nondiagnostic on biopsy, the risk of malignancy is unknown but is probably closer to 5%–10% (29).

R24. For patients with an isolated indeterminate solitary nodule who prefer a more limited surgical procedure, thyroid lobectomy is the recommended initial surgical approach—Recommendation C

R25. Because of an increased risk for malignancy, total thyroidectomy is indicated in patients with large tumors (> 4 cm) when marked atypia is seen on biopsy, when the biopsy reading is "suspicious for papillary carcinoma," in patients with a family history of thyroid carcinoma, and in patients with a history of radiation exposure (32,93,94). Patients with bilateral nodular disease or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of requiring a future surgery on the contralateral lobe should also undergo total thyroidectomy—Recommendation A

Surgery for a biopsy diagnostic for malignancy. Near-total or total thyroidectomy is recommended if any of the following are present: the primary thyroid carcinoma is more than 1–1.5 cm, contralateral thyroid nodules, regional or distant metastases, patient has a personal history of radiation therapy to the head and neck, or a first-degree family history of differentiated thyroid cancer. Older age (> 45 years) may also be a criterion for recommending near-total or total thyroidectomy because of higher recurrence rates in this age group (62,68,69,95,96). Increased extent of primary surgery may improve survival for high-risk patients (97–99), while

rates of recurrence are reduced by total- or near-total thyroidectomy even among low-risk patients (68,100,101).

R26. For most patients with thyroid cancer, the initial surgical procedure should be a near-total or total thyroidectomy. Thyroid lobectomy alone may be sufficient treatment for small, low-risk, isolated, intrathyroidal papillary carcinomas in the absence of cervical nodal metastases—Recommendation A

Lymph node dissection. Regional lymph node metastases are present at the time of diagnosis in 20%–90% of patients with papillary carcinoma and a lesser proportion of patients with other histotypes (75,102). In many cases, these lymph nodes do not appear abnormal to inspection (103). Bilateral central (compartment VI) node dissection may improve survival (compared to historic controls) and reduce the risk for nodal recurrence (76,103). This central compartment dissection can be achieved with low morbidity in experienced hands (104–107).

R27. Routine central-compartment (level VI) neck dissection should be considered for patients with papillary thyroid carcinoma and suspected Hürthle carcinoma. Near-total or total thyroidectomy without central node dissection may be appropriate for follicular cancer, and when followed by radioactive iodine therapy, may provide an alternative approach for papillary and Hürthle cell cancers—Recommendation B

Lymph nodes in the lateral neck (compartments II–IV) and posterior triangle (compartment V) may also be involved by thyroid cancer, most often in papillary and Hürthle cell carcinoma (75,108). For those patients in whom nodal disease is evident clinically, on preoperative ultrasound, or at the time of surgery, surgical resection may reduce the risk of recurrence and possibly mortality (102,109,110). Functional compartmental en-bloc dissection is favored over selective dissection (berry picking) with limited data suggesting improved mortality (64,111–113).

R28. Lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic cervical lymphadenopathy detected clinically or by imaging, especially when they are likely to fail radioactive iodine treatment based on lymph node size, number, or other factors, such as aggressive histology of the primary tumor—Recommendation B

Completion thyroidectomy. Completion thyroidectomy may be necessary when the diagnosis of malignancy is made after lobectomy for an indeterminate or nondiagnostic biopsy. Some patients with malignancy may require completion thyroidectomy to provide complete resection of multicentric disease (114), and to allow radioiodine therapy. Most (115,116) but not all (114) studies of papillary cancer have observed a higher rate of cancer in the opposite lobe when multifocal ($\geq$ 2 foci), as opposed to unifocal, disease is present in the ipsilateral lobe. The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of a near-total or total thyroidectomy (117,118).

R29. Completion thyroidectomy should be offered to those patients for whom a near-total or total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery. This includes all patients with thyroid cancer except those with small ($<$ 1 cm), intrathyroidal, node-negative, low-risk tumors—Recommendation B

R30. Ablation of the remaining lobe with radioactive iodine has been used as an alternative to completion thyroidectomy (119). It is unknown whether this approach results in similar long term outcomes. Consequently, radioactive iodine ablation in lieu of completion thyroidectomy is not recommended—Recommendation E

What is the role of postoperative staging systems and which should be used?

The role of postoperative staging. Postoperative staging for thyroid cancer, as for other cancer types, is used: (1) to permit prognostication for an individual patient with differentiated thyroid carcinoma; (2) to tailor decisions regarding postoperative adjunctive therapy, including radioiodine therapy and thyrotropin suppression, to the patient's risk for disease recurrence and mortality; (3) to make decisions regarding the frequency and intensity of follow-up, directing more intensive follow-up towards patients at highest risk; and (4) to enable accurate communication regarding a patient between health care professionals. Staging systems also allow evaluation of differing therapeutic strategies applied to comparable groups of patients in clinical studies.

AJCC/UICC TNM staging. Application of the AJCC/UICC classification system based on pTNM parameters is recommended for tumors of all types, including thyroid cancer (67,120), because it provides a useful shorthand method to describe the extent of the tumor (121) (Table 2). This classification is also used for hospital cancer registries and epidemiologic studies. In thyroid cancer, the AJCC/UICC Stage does not take account of several additional independent prognostic variables and may risk misclassification of some patients. Numerous other schemes have been developed in an effort to achieve more accurate risk factor stratification, including CAEORTC, AGES, AMES, U of C, MACIS, OSU, MSKCC, and NTCTCS systems (61,62,68,98,122–125). These schemes take into account a number of factors identified as prognostic for outcome in multivariate analysis of retrospective studies, with the most predictive factors generally being regarded as the presence of distant metastases, the age of the patient, and the extent of the tumor. These and other risk factors are weighted differently among these systems according to their importance in predicting outcome but no scheme has demonstrated clear superiority (125). Nevertheless, each of the schemes allows accurate identification of the majority (70%–85%) of patients at low-risk of mortality, allowing the follow-up and management of these patients to be less intensive than the higher risk minority, who may benefit from a more aggressive management strategy.

R31. Because of its utility in predicting disease mortality, and its requirement for cancer registries, AJCC/UICC staging is

recommended for all patients with differentiated thyroid cancer. The use of postoperative clinicopathologic staging systems is also recommended to improve prognostication and to plan follow-up for patients with differentiated thyroid carcinoma—Recommendation B

What is the role of postoperative radioiodine remnant ablation?

Postoperative radioiodine remnant ablation is increasingly being used to eliminate the post-surgical thyroid remnant. The goals of this treatment are to destroy residual thyroid tissue in an effort to decrease the risk for recurrent locoregional disease and to facilitate long-term surveillance with whole-body iodine scans and/or stimulated thyroglobulin measurements (62,63). A number of large, retrospective studies show a significant reduction in the rates of disease recurrence (61,98,99,126) and cause-specific mortality (98,99,126–128). However, other similar studies show no such benefit, at least among the majority of patients with papillary thyroid carcinoma, who are at the lowest risk for mortality (68,101,128–131). In those studies that show benefit, the advantage appears to be restricted to patients with larger tumors (> 1.5 cm), or with residual disease after surgery, while lower risk patients do not show evidence for benefit (68,98,132). No prospective studies have been performed to address this question (128).

R32. Radioiodine ablation is recommended for patients with stages III and IV disease (AJCC sixth edition; Table 2), all patients with stage II disease younger than age 45 years and most patients with stage II disease 45 years or older, and selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies—Recommendation B

How should patients be withdrawn from thyroid hormone prior to radioiodine ablation?

Remnant ablation (as well as subsequent monitoring for thyroid cancer persistence/recurrence using radioiodine

Table 2. TNM Classification System for Differentiated Thyroid Carcinoma

Definition		
T1	Tumor diameter 2 cm or smaller	
T2	Primary tumor diameter > 2 to 4 cm	
T3	Primary tumor diameter > 4 cm limited to the thyroid or with minimal extrathyroidal extension	
$T4_a$	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	
$T4_b$	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels	
TX	Primary tumor size unknown, but without extrathyroidal invasion	
NO	No metastatic nodes	
$N1_a$	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)	
$N1_b$	Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal mode metastases	
NX	Nodes not assessed at surgery	
MO	No distant metastases	
M1	Distant metastases	
MX	Distant metastases not assessed	
Stages		
	Patient age < 45 years	*Patient aged 45 years or older*
Stage I	Any T, any N, MO	T1, NO, MO
Stage II	Any T, any N, M1	T2, NO, MO
Stage III		T3, NO, MO T1, $N1_a$, MO T2, $N1_a$, MO T3, $N1_a$, MO
Stage IVA		$T4_a$, NO, MO $T4_a$, $N1_a$, MO T1, $N1_b$, MO T2, $N1_b$, MO T3, $N1_b$, MO $T4_a$, $N1_b$, MO
Stage IVB		$T4_b$, Any N, MO
Stage IVC		Any T, Any N, M1

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The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002). Published by Springer-Verlag, New York, Inc.

whole-body scans (WBS) and/or serum thyroglobulin measurement) requires TSH stimulation. No controlled studies have been performed to assess adequate levels of endogenous TSH for optimal ablation therapy or follow-up testing. Noncontrolled studies suggest that a TSH of more than 30 mU/L is associated with increased radioiodine uptake in tumors (133), while studies using single-dose exogenous TSH suggest maximal thyrocyte stimulation at TSH levels between 51–82 mU/L (134,135). Endogenous TSH elevation can be achieved by two basic approaches to thyroid hormone withdrawal, stopping levothyroxine (LT_4) and switching to levotriiodothyronine (LT_3) for 2–4 weeks followed by withdrawal of triiodothyronine (T_3) for 2 weeks, or discontinuation of LT_4 for 3 weeks without use of T_3. Both methods of preparation can achieve serum TSH levels greater than 30 mU/L in greater than 90% of patients (135–144). These two approaches have not been directly compared for efficiency of patient preparation (efficacy of ablation, iodine uptake, thyroglobulin levels, disease detection, or symptoms). Other preparative approaches have been proposed, but have not been validated by other investigators (145,146).

R33. Patients undergoing radioiodine therapy or diagnostic testing can be prepared by LT_4 withdrawal for at least 3 weeks or T_3 treatment for 2–4 weeks and T_3 withdrawal for 2 weeks with measurement of serum TSH to determine timing of testing or therapy (TSH $>$ 30 mU/L)—Recommendation B

Should radioiodine scanning be performed before radioiodine ablation?

Radioiodine WBS provides information on the presence of iodine-avid thyroid tissue, which may represent the normal thyroid remnant or the presence of residual disease in the postoperative setting. In the presence of a large thyroid remnant, the scan is dominated by uptake within the remnant, potentially masking the presence of extrathyroidal disease within locoregional lymph nodes, the upper mediastinum or even at distant sites, reducing the sensitivity of disease detection (147). Furthermore, there is an increasing trend to avoid pretherapy radioiodine scans altogether because of concerns over ^{131}I-induced stunning of thyroid cancer (148). Stunning is defined as a reduction in uptake of the ^{131}I therapy dose induced by a pretreatment diagnostic dose. Stunning occurs most prominently with higher doses (5–10 mCi) of ^{131}I (149), with increasing time between the diagnostic dose and therapy (150), and is not visually appreciated at lower doses (1–3 mCi). However, the accuracy of low-dose ^{131}I scans has been questioned, and some have reported quantitatively the presence of stunning below the threshold of visual detection (151). Although comparison studies show excellent concordance between ^{123}I and ^{131}I for tumor detection, optimal ^{123}I activity and time to scan after ^{123}I administration is not known (152). Furthermore, ^{123}I is expensive, is not universally available, its short half life ($t_{1/2}$ = 13 hours) makes handling this isotope more difficult (153), and stunning may also occur though to a lesser degree than with ^{131}I (150). Determination of the thyroid bed uptake can be achieved using 10–100 μCi ^{131}I.

R34. Pretherapy scans and/or measurement of thyroid bed uptake may be useful when the extent of the thyroid remnant cannot be accurately ascertained from the surgical report or neck ultrasonography, or when the results would alter either the decision to treat or the activity of radioiodine that is administered. If performed, pretherapy scans should utilize low-dose ^{131}I (1–3 mCi) or ^{123}I—Recommendation C

What activity of ^{131}I should be used for remnant ablation?

Successful remnant ablation is usually defined as an absence of visible radioiodine uptake on a subsequent diagnostic radioiodine scan. Activities between 30 and 100 mCi of ^{131}I generally show similar rates of successful remnant ablation (154–157), although there is a trend toward higher success rates with higher activities (158).

R35. The minimum activity (30–100 mCi) necessary to achieve successful remnant ablation should be chosen, particularly for low-risk patients—Recommendation B

R36. If residual microscopic disease is suspected or documented, or if there is a more aggressive tumor histology (e.g. tall cell, insular, columnar cell carcinoma) , then higher activities (100– 200 mCi) may be appropriate—Recommendation C

Can recombinant human thyrotropin (Thyrogen™) be used in lieu of thyroxine withdrawal for remnant ablation?

There is limited experience with the use of recombinant human thyrotropin (rhTSH) in radioiodine ablation of postsurgical thyroid remnants. Some patients, unable to tolerate hypothyroidism or unable to generate an elevated TSH, have undergone successful remnant ablation with rhTSH (159,160). Successful remnant ablation with 30 mCi ^{131}I was equivalent after thyroxine withdrawal compared to rhTSH stimulation when the thyroxine therapy was stopped 1 day prior to the rhTSH injections and restarted the day after ^{131}I therapy (161). rhTSH is not approved in the United States for this indication, but it is approved in Europe.

R37. Remnant ablation can be performed following thyroxine withdrawal or rhTSH stimulation—Recommendation B[a]

Is a low-iodine diet necessary before remnant ablation?

The efficacy of radioactive iodine depends on the radiation dose delivered to the thyroid tissue (162). Low-iodine diets ($<$ 50 μg/d of dietary iodine) have been recommended prior to radioiodine therapy (162–164), to increase the effective radiation dose. Measurement of iodine excretion may be a useful way to identify patients whose iodine intake could interfere with radioiodine remnant ablation (164).

R38. A low-iodine diet for 1–2 weeks is recommended for patients undergoing radioiodine remnant ablation, particularly for those patients with high iodine intake—Recommendation B

[a]Note: Because of varying degrees of involvement with Genzyme Corporation, the manufacturer of rhTSH (Thyrogen), the following authors recused themselves from the discussion of this recommendation: Bryan Haugen, M.D.; Richard Kloos, M.D.; Ernest Mazzaferri, M.D.; Steven Sherman, M.D.; and R. Michael Tuttle, M.D.

Should a posttherapy scan be performed after remnant ablation?

Posttherapy whole body iodine scanning is typically conducted approximately 1 week after radioactive iodine therapy to visualize metastases. Additional metastatic foci have been reported in 10%–26% of patients scanned after high-dose radioiodine treatment compared to the diagnostic scan (165,166). The new abnormal uptake was found most often in the neck, lungs and mediastinum, and the newly discovered disease altered the disease stage in approximately 10% of the patients, affecting clinical management in 9%–15% (165–167).

R39. A posttherapy scan is recommended after radioiodine remnant ablation. This is typically done 5–8 days after the therapeutic dose is administered, although published data supporting this time interval are lacking—Recommendation B

What is the role of TSH suppression therapy?

Differentiated thyroid cancer expresses the thyrotropin receptor on the cell membrane, and responds to TSH stimulation by increasing the expression of several thyroid-specific proteins (thyroglobulin, sodium iodide symporter) and by increasing the rates of cell growth. Suppression of TSH, using supraphysiologic doses of LT_4, is used commonly to treat patients with thyroid cancer in an effort to decrease the risk of recurrence (73,168). A recent meta-analysis supported the efficacy of TSH suppression therapy in preventing major adverse clinical events (relative risk [RR] = 0.73; confidence interval [CI] = 0.60–0.88; $p < 0.05$) (168).

What is the appropriate degree of initial TSH suppression?

Retrospective studies have demonstrated that TSH suppression to below 0.1 mU/L may improve outcomes in high-risk patients with thyroid cancer (73,169), although no such evidence of benefit has been documented in low-risk patients. Adverse effects of TSH suppression may include the known consequences of subclinical thyrotoxicosis, including exacerbation of angina in patients with ischemic heart disease, increased risk for atrial fibrillation, and increased risk of osteoporosis in postmenopausal women (170).

R40. Initial thyrotropin suppression to below 0.1 mU/L is recommended for high-risk patients with thyroid cancer, while maintenance of the TSH at or slightly below the lower limit of normal (0.1–0.5 mU/L) is appropriate for low-risk patients—Recommendation B

Is there a role for adjunctive external beam irradiation or chemotherapy?

External beam irradiation. External beam irradiation is used infrequently in the management of thyroid cancer except as a palliative treatment for locally advanced, otherwise unresectable disease (171). There are reports of responses among patients with locally advanced disease (172,173), and improved relapse-free and cause-specific survival (174). It remains unknown whether external beam radiation might reduce the risk for recurrence in the neck after adequate primary surgery and/or radioiodine treatment.

R41. The use of external beam irradiation should be considered in patients over age 45 with grossly visible extrathyroidal extension at the time of surgery and a high likelihood of microscopic residual disease, and for those patients with gross residual tumor in whom further surgery or radioactive iodine would likely be ineffective—Recommendation B

Chemotherapy. There are no data to support the use of adjunctive chemotherapy in the management of differentiated thyroid cancer. Doxorubicin (adriamycin) may act as a radiation sensitizer in some tumors of thyroid origin (175,176), and could be considered for patients with locally advanced disease undergoing external beam radiation.

R42. There is no role for the routine adjunctive use of chemotherapy in patients with differentiated thyroid cancer—Recommendation F

Differentiated Thyroid Cancer: Long-Term Management

What are the appropriate features of long-term management?

Accurate surveillance for possible recurrence in patients thought to be free of disease is a major goal of long-term follow up. Tests with high negative predictive value allow identification of patients unlikely to experience disease recurrence, so that less aggressive management strategies can be used that may be more cost effective and safe. Similarly, patients with a higher risk of recurrence are monitored more aggressively, based on the admittedly unproven premise, that early detection of recurrent disease offers the best opportunity for effective treatment. Patients with persistent or recurrent disease are offered treatment to cure or to delay future morbidity or mortality. In the absence of such options, therapies to palliate by substantially reducing tumor burden or preventing tumor growth are utilized, with special attention paid to tumor-threatening critical structures.

Follow-up is different for patients at low, intermediate, and at high risk of having persistent or recurrent disease. AJCC-IUCC staging was developed to predict risk for death, not recurrence. For assessment of risk of recurrence, a three level stratification can be used. Low-risk patients have the following characteristics after initial surgery and remnant ablation: no local or distant metastases; all macroscopic tumor has been resected, there is no tumor invasion of locoregional tissues or structures, the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion, and, if ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the first posttreatment whole-body radioiodine scan (RxWBS) (177–179). Intermediate-risk patients have microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery or tumor with aggressive histology or vascular invasion (180–182). High-risk patients have macroscopic tumor invasion, incomplete tumor resection, distant metastases, or ^{131}I uptake outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation (183,184).

What is the appropriate method of following patients after surgery with or without remnant ablation?

Criteria for absence of persistent tumor. In patients who have undergone total or near-total thyroidectomy and thyroid remnant ablation, disease free status comprises all of the following: no clinical evidence of tumor, no imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment whole body scan, on a recent diagnostic scan or neck ultrasound), and undetectable serum thyroglobulin levels during TSH suppression and stimulation in the absence of interfering antibodies (Figs. 2 and 3).

What is the role of serum thyroglobulin assays in the follow-up of differentiated thyroid cancer?

Measurement of serum thyroglobulin levels is an important modality to monitor patients for residual or recurrent disease. Serum thyroglobulin has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest degrees of sensitivity noted after thyroid hormone withdrawal or stimulation using recombinant human thyrotropin (rhTSH) (185). Serum thyroglobulin measurements obtained during thyroid hormone suppression of TSH may fail to identify patients with relatively small amounts of residual tumor (177,186). Conversely, even TSH-stimulated thyroglobulin measurement may fail to identify patients with clinically significant tumor, because of antithyroglobulin antibodies, or less commonly, defective or absent production and secretion of immunoreactive thyroglobulin by tumor cells (187). Thyroglobulin levels should be interpreted in light of the pretest probability of clinically significant residual tumor. An aggressive or poorly differentiated tumor may be present despite low basal or stimulated thyroglobulin; in contrast, a minimally elevated stimulated thyroglobulin may occur in patients at low risk for clinically significant morbidity (188).

Initial follow-up for low-risk patients (approximately 85% of postoperative patients) who have undergone total or near-total thyroidectomy and ^{131}I remnant ablation should be based mainly on TSH-suppressed thyroglobulin and cervical ultrasound, followed by TSH-stimulated serum thyroglobulin measurements if the TSH-suppressed thyroglobulin testing is undetectable (177,186).

Approximately 20% of patients who are clinically free of disease with serum thyroglobulin levels less than 1 ng/mL during thyroid hormone suppression of TSH (186) will have a serum thyroglobulin level greater than 2 ng/mL after rhTSH or thyroid hormone withdrawal. In approximately one third of this group, persistent tumor can be identified on imaging studies. There is good evidence that a thyroglobulin cutoff level above 2 ng/mL after rhTSH stimulation is highly sensitive in identifying patients with persistent tumor (186,189–194). However, the results of serum thyroglobulin measurements made on the same serum specimen differ among laboratories (88). Therefore, the thyroglobulin cutoff may differ slightly among medical centers and laboratories. Furthermore, the clinical significance of minimally detectable thyroglobulin levels is unclear, especially if only detected after TSH stimulation.

The presence of antithyroglobulin antibodies, which occur in approximately 25% of thyroid cancer (195) patients and 10% of the general population (196), will falsely lower serum thyroglobulin determinations in immunometric assays (197). The use of recovery assays for this purpose is controversial (184,198). Serial serum antithyroglobulin antibody measurements may serve as an imprecise surrogate marker of residual normal thyroid tissue or tumor (198,199). Serum thyroglobulin measurements are less sensitive in patients with small cervical lymph node metastases or less differentiated tumor (184,200). A rising unstimulated or stimulated serum thyroglobulin may indicate disease that is likely to become clinically apparent (201,202).

R43. Serum thyroglobulin should be measured every 6–12 months by an immunometric assay, ideally in the same laboratory and using the same assay, during follow-up of patients with differentiated thyroid carcinoma who have undergone total or near-total thyroidectomy and thyroid remnant ablation. Thyroglobulin antibodies should be quantitatively assessed with every measurement of serum thyroglobulin—Recommendation A

R44. Periodic serum thyroglobulin measurements should be considered during follow-up of patients with differentiated thyroid carcinoma who have undergone less than total thyroidectomy, and in patients who have had a total thyroidectomy but not radioiodine ablation. The cutoff levels to detect tumor during TSH suppression or stimulation are not known, but unstimulated or stimulated levels greater than 2 ng/mL that increase over time may represent recurrent disease—Recommendation C

R45. In low risk patients who have had remnant ablation and negative cervical ultrasound and TSH-suppressed thyroglobulin 6 months after treatment, serum thyroglobulin should be measured after thyroxine withdrawal or rhTSH stimulation approximately 12 months after the ablation to verify absence of disease. The timing or necessity of subsequent stimulated testing is uncertain for those found to be free of disease—Recommendation A

What are the roles of diagnostic whole-body radioiodine scans, ultrasound, and other imaging techniques during follow-up of differentiated thyroid cancer?

Diagnostic whole-body radioiodine scans. There are two main issues that affect the use of diagnostic whole body radioiodine scans (DxWBS) during follow-up: stunning (described above) and accuracy. A DxWBS is most useful during follow-up when there is little or no remaining normal thyroid tissue. Disease not visualized on the DxWBS, regardless of the activity of ^{131}I used, may occasionally be visualized on the RxWBS images done after larger, therapeutic amounts of ^{131}I (186,203–206). After radioiodine ablation, subsequent DxWBS have low sensitivity and are usually not necessary in low-risk patients who are clinically free of residual tumor and have an undetectable serum thyroglobulin level during thyroid hormone suppression of serum TSH and negative cervical ultrasound (177,183,186,205,207).

R46. After the first RxWBS performed after radioiodine remnant ablation, low-risk patients with negative TSH-stimulated thyroglobulin and cervical ultrasound do not require routine DxWBS during follow-up—Recommendation A

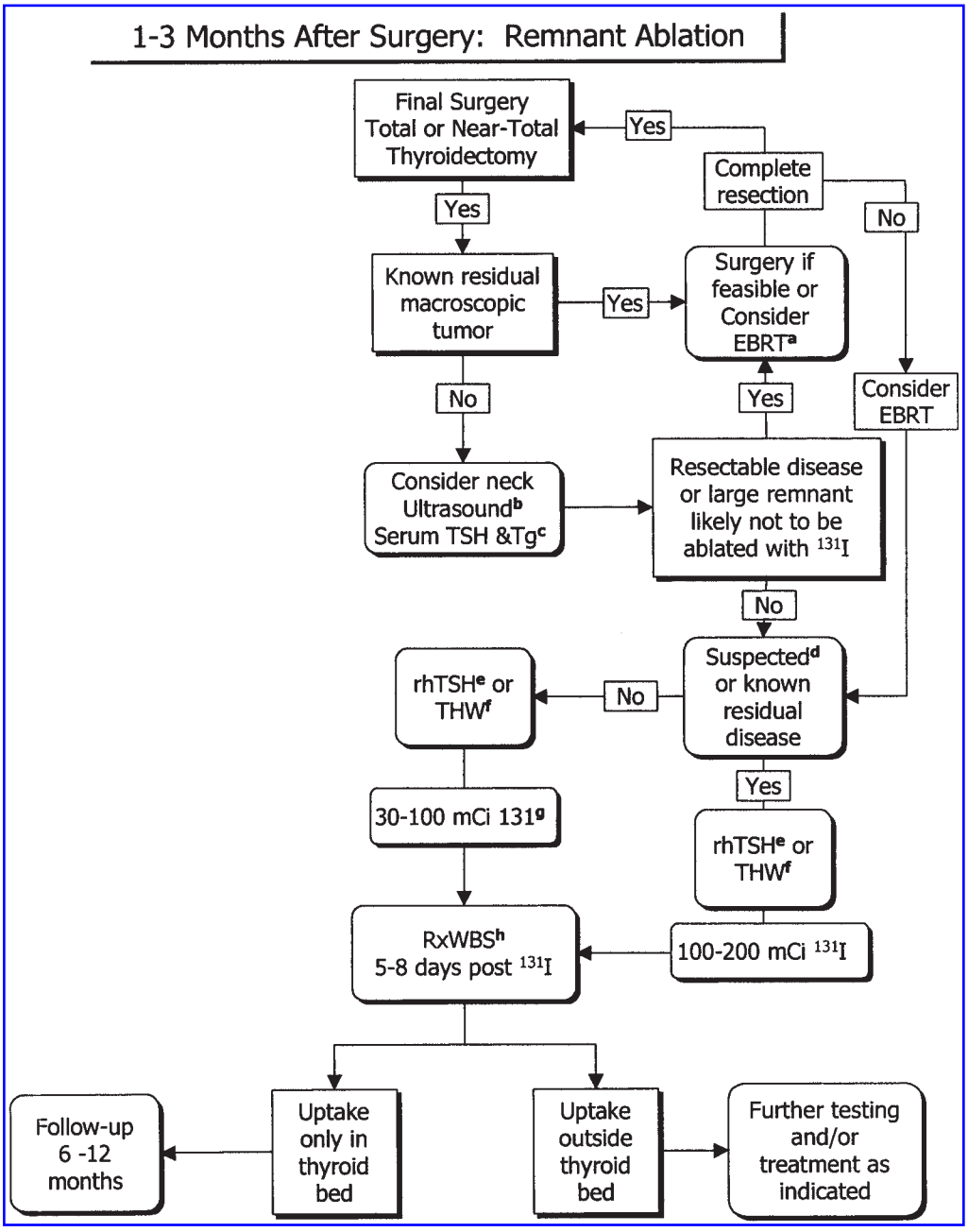

FIG. 2. Algorithm for initial follow-up of patients with differentiated thyroid carcinoma. [a]EBRT is external beam radiotherapy. The usual indication for EBRT is macroscopic unresectable tumor in a patient older than 45 years. [b]Neck ultrasonography of operated cervical compartments is often compromised for several months after surgery. [c]Tg is thyroglobulin with antithyroglobulin antibody measurement; serum Tg is usually measured by immunometric assay and may be falsely elevated for several weeks by injury from surgery or by heterophile antibodies, although a very high serum Tg level after surgery usually indicates residual disease. [d]Some clinicians suspect residual disease when malignant lymph nodes, or tumors with aggressive histologies (as defined in the text) have been resected, or when there is a microscopically positive margin of resection. [e]rhTSH is recombinant human thyrotropin, which is not Food and Drug Administration (FDA)-approved in the United States for preparing patients for therapy, but was approved in 2005 for remnant ablation in Europe, and is administered as follows: 0.9 mg rhTSH intramuscularly on 2 consecutive days, followed by ^{131}I therapy on third day. [f]THW is levothyroxine and/or triiodothyronine withdrawal. [g]See text for exceptions regarding remnant ablation. DxWBS (diagnostic whole body scintigraphy) is not usually necessary at this point, but may be performed if the outcome will change the decision to treat with radioiodine and/or the amount of administered activity. [h]RxWBS is posttreatment whole-body scan done 5 to 8 days after therapeutic ^{131}I administration. (Modified from J Nucl Med, 46:1079–1088, 2005. Reprinted with permission.)

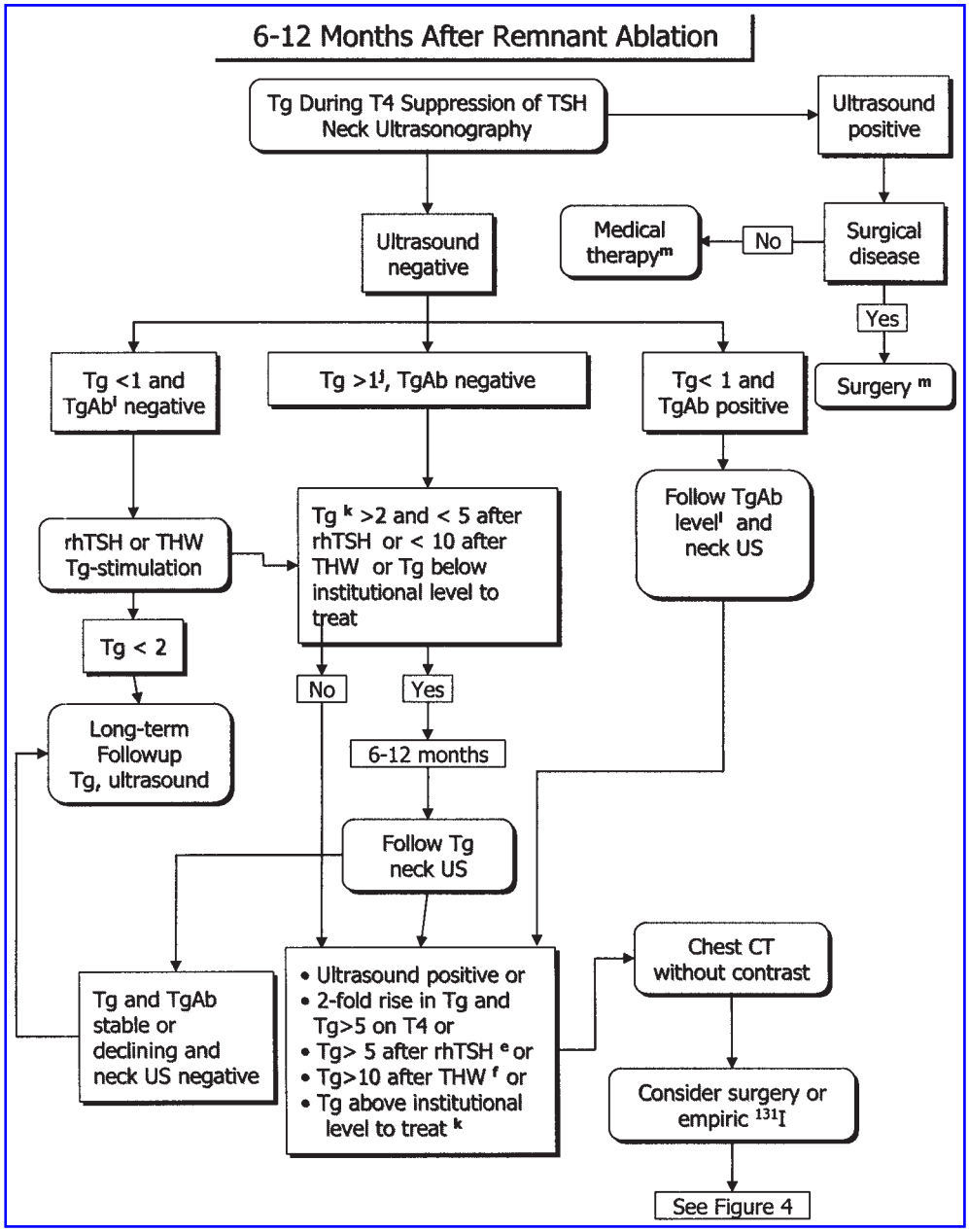

FIG. 3. Longer term follow-up of patients with differentiated thyroid carcinoma. [i]TgAb is antithyroglobulin antibody usually measured by immunometric assay. [j]Heterophile antibodies may be a cause of falsely elevated serum Tg levels. (Preissner CM, Dodge LA, O'Kane DJ, Singh RJ, Grebe SK 2005 Prevalence of heterophilic antibody interference in eight automated tumor marker immunoassays. Clin Chem **51:**208–210; Preissner CM, O'Kane DJ, Singh RJ, Morris JC, Grebe SK 2003 Phantoms in the assay tube: heterophile antibody interferences in serum thyroglobulin assays. J Clin Endocrinol Metab **88:**3069–3074.) The use of heterophile blocking tubes or heterophile blocking reagents have reduced, but not completely eliminated this problem. Tg that rises with thyrotropin (TSH) stimulation and falls with TSH suppression is unlikely to result from heterophile antibodies. [k]See text concerning further information regarding levels of Tg at which therapy should be considered. [l]Tg radioimmunoassay (RIA) may be falsely elevated or suppressed by TgAb. Tg results following TSH stimulation with recombinant human thyrotropin (rhTSH) or thyroid hormone withdrawal are invalidated by TgAb in the serum even when Tg is measured by most RIA tests. TgAb levels often decline to undetectable levels over years following surgery (Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, Grasso L, Pinchera A 2003 Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med **139:**346–351). A rising level of TgAb may an early indication of recurrent disease (Spencer CA, Takeuchi M, Kazarosyan M, Wang CC, Guttler RB, Singer PA, Fatemi S, LoPresti JS, Nicoloff JT 1998 Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab **83:**1121–1127). [m]See text for decision regarding surgery versus medical therapy, and surgical approaches to locoregional metastases. Fine-needle aspiration confirmation of malignancy is generally advised. Preoperative chest computed tomography (CT) is recommended as distant metastases may change management. (Modified from J Nucl Med, 46:1079–1088, 2005. Reprinted with permission.)

R47. DxWBS 6–12 months after remnant ablation may be of value in the follow-up of patients with high or intermediate risk of persistent disease, but should be done with low dose ^{131}I or ^{123}I—Recommendation C

Cervical ultrasonography. Cervical ultrasonography is highly sensitive in the detection of cervical metastases in patients with differentiated thyroid cancer (208). Cervical metastases occasionally may be detected by neck ultrasonography even when TSH-stimulated serum thyroglobulin levels remain undetectable (200).

R48. After surgery, cervical ultrasound to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6 and 12 months and then annually for at least 3–5 years, depending on the patients' risk for recurrent disease and thyroglobulin status—Recommendation B

What is the role of thyroxine suppression in long-term follow-up of differentiated thyroid cancer?

A meta-analysis has suggested an association (168) between thyroid hormone suppression therapy and reduction of major adverse clinical events. The appropriate degree of TSH suppression by LT_4 is still unknown. One study found that a constantly suppressed TSH (≤ 0.05 μU/mL) was associated with a longer relapse-free survival than when serum TSH levels were always 1 μU/mL or greater, and that the degree of TSH suppression was an independent predictor of recurrence in multivariate analysis (169). Conversely, another large study found that disease stage, patient age, and ^{131}I therapy independently predicted disease progression, but that the degree of TSH suppression did not (73). A third study showed that during LT_4 therapy the mean thyroglobulin levels were significantly higher when TSH levels were normal than when TSH levels were suppressed ($<$ 0.5 mU/L) but only in patients with local or distant relapse (209).

R49. In patients with persistent disease, the serum TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications—Recommendation B

R50. In patients who are clinically free of disease but who presented with high risk disease, consideration should be given to maintaining TSH suppressive therapy to achieve serum TSH levels of 0.1 to 0.5 mU/L for 5–10 years—Recommendation C

R51. In patients free of disease, especially those at low risk for recurrence, the TSH may be kept within the low normal range (0.3 to 2 mU/L)—Recommendation C

What is the most appropriate management of patients with metastatic disease?

Metastases discovered during follow-up are likely manifestations of persistent disease that has survived initial treatment, and are often incurable by additional ^{131}I treatment. Some patients will have a reduction in tumor burden with additional treatments that may offer a survival or palliative benefit (204,210–212).

The preferred hierarchy of treatment for metastatic disease (in order) is surgical excision of locoregional disease in potentially curable patients, ^{131}I therapy, external beam radiation, watchful waiting with patients with stable asymptomatic disease, and experimental chemotherapy trials. Experimental trials may be tried before external beam radiation in special circumstances, in part because of the morbidity of external beam radiation and its relative lack of efficacy. A small fraction of patients may benefit from radiofrequency ablation (213), ethanol ablation (214), or chemoembolization (215).

Surgical management of locoregional metastases. Surgery is favored for locoregional (i.e., cervical lymph nodes and/or soft tissue tumor in the neck) recurrences, when distant metastases are not present. Approximately one third to one half of patients may become free of disease in short-term follow-up (216). It is not clear that treatment of locoregional disease is beneficial in the setting of untreatable distant metastases, except for possible palliation of symptoms or prevention of airway or aero-digestive obstruction. Impalpable metastatic lymph nodes, visualized on ultrasound or other anatomic imaging modality, have survived initial ^{131}I therapy and should be considered for resection. Most surgeons endorse complete ipsilateral compartmental dissection of involved compartments with persistent/recurrent disease while sparing vital structures (e.g., ipsilateral central neck dissection [level VI], or modified neck dissection [levels II–V sparing the spinal accessory nerve, the internal jugular vein, and sternocleidomastoid muscle]) (217) as opposed to berry picking or selective lymph node resection procedures or ethanol ablation (214), because microscopic lymph node metastases are commonly more extensive than would appear from imaging studies alone (112,218,219).

R52. Patients with persistent/recurrent disease confined to the neck should undergo complete ipsilateral or central compartmental dissection of involved compartments while sparing vital structures—Recommendation B

Surgical management of aero-digestive invasion. For tumors that invade the upper aero-digestive tract, surgery combined with additional therapy such as ^{131}I and/or external beam radiation is generally advised (220,221). Patient outcome is related to complete resection of all gross disease with the preservation of function, with techniques ranging from shaving tumor off the trachea or esophagus for superficial invasion, to more aggressive techniques when the trachea is more deeply invaded (e.g., direct intraluminal invasion) including tracheal resection and anastomosis (222–224) or esophagopharyngectomy. Patients who are not curable may undergo less aggressive local treatment. Tracheal stents and tracheotomy can improve quality of life. Laser therapy is indicated in cases of asphyxia or significant hemoptysis and as a preliminary step prior to subsequent radical or palliative treatments (221).

R53. When technically feasible, surgery for aero-digestive disease is recommended in combination with radioiodine and/or external beam radiotherapy—Recommendation B

Radioiodine therapy for locoregional or distant metastatic disease. For regional nodal metastases discovered on

DxWBS, radioiodine is usually used, although surgery is typically used in the presence of bulky disease or disease amenable to surgery found on anatomic imaging such as ultrasound, CT scanning or MRI. Radioiodine is also used adjunctively after surgery for regional nodal disease or aerodigestive invasion if residual disease is present or suspected.

Methods of administering ^{131}I for locoregional or metastatic disease. Despite the apparent effectiveness of ^{131}I therapy in many patients, the optimal therapeutic activity remains uncertain and controversial (225). There are three approaches to ^{131}I therapy: empiric fixed amounts, therapy determined by the upper bound limit of blood and body dosimetry, and quantitative tumor dosimetry (226). Dosimetric methods are often reserved for patients with distant metastases or unusual situations such as renal failure or when therapy with rhTSH stimulation is deemed necessary. Comparison of outcome among these methods from published series is difficult (227). No prospective randomized trial to address the optimal therapeutic approach has been published. Arguments in favor of higher activities cite a positive relationship between the total ^{131}I uptake per tumor mass and outcome (141), while others have not confirmed this relationship (227,228).

R54. In the treatment of locoregional or metastatic disease, no recommendation can be made about the superiority of one method of radioiodine administration over another (empiric high dose versus blood or body dosimetry)—Recommendation I

rhTSH in the management of recurrent or metastatic disease. No randomized trial comparing thyroid hormone withdrawal therapy to rhTSH-mediated therapy has been reported, despite a growing body of nonrandomized studies regarding this use (229–237). The use of rhTSH does not eliminate and may even increase the possibility of rapid swelling of metastatic lesions (234,238–240). Many of these case reports and series report disease stabilization or improvement in some patients after rhTSH-mediated ^{131}I therapy.

R55. There are currently insufficient outcome data to recommend rhTSH-mediated therapy for all patients with metastatic disease being treated with ^{131}I—Recommendation D

R56. rhTSH-mediated therapy may be indicated in selected patients with underlying comorbidities making iatrogenic hypothyroidism potentially risky, in patients with pituitary disease who are unable to raise their serum TSH, or in patients in whom a delay in therapy might be deleterious—Recommendation C

The use of lithium in ^{131}I therapy. Lithium inhibits iodine release from the thyroid without impairing iodine uptake, thus enhancing ^{131}I retention in normal thyroid and tumor cells (241). One study (242) found that lithium increased the estimated ^{131}I radiation dose in metastatic tumors an average of more than twofold, but primarily in those tumors that rapidly cleared iodine (242).

R57. Because there are no outcome data that demonstrate a better outcome of patients treated with ^{131}I in the setting of lithium therapy, the committee cannot recommend for or against its use—Recommendation I

Treatment of distant metastatic disease. The overall approach to treatment of distant metastatic thyroid cancer is based upon the following observations and oncologic principles:

1. Morbidity and mortality are increased in patients with distant metastases, but individual prognosis depends upon factors including distribution and number of sites of metastasis (e.g., brain, bone, lung), tumor burden, and age at diagnosis of metastases (212,237,243–249).
2. Improved survival is associated with responsiveness to surgery and/or radioiodine (212,237,243–249).
3. In the absence of demonstrated survival benefit, certain interventions can provide significant palliation or reduce morbidity (216,250–252).
4. In the absence of improved survival, palliative benefit or reduced potential morbidity, the value of empiric therapeutic intervention is significantly limited by the potential for toxicity.
5. Treatment of a specific metastatic area must be considered in light of the patient's performance status and other sites of disease (e.g., 5%–20% of patients with distant metastases die from progressive cervical disease (249,253).
6. Longitudinal reevaluation of patient status and continuing reassessment of potential benefit and risk of intervention is required.
7. The overall poor outcome of patients with radiographically evident or symptomatic metastases that do not respond to radioiodine, the complexity of multidisciplinary treatment considerations and the availability of prospective clinical trials should encourage the clinician to refer such patients to tertiary centers with particular expertise.

Treatment of pulmonary metastases. In the management of the patient with pulmonary metastases, key criteria for therapeutic decisions include size of metastatic lesions (macronodular typically detected by chest radiography; micronodular typically detected by CT; lesions beneath the resolution of CT); avidity for radioiodine and, if applicable, response to prior radioiodine therapy; and stability (or lack thereof) of metastatic lesions. Pulmonary pneumonitis and fibrosis are rare complications of high dose radioactive iodine treatment. Dosimetry studies with a limit of 80 mCi whole-body retention at 48 hours and 200 cGy to the red bone marrow should be considered in patients with diffuse ^{131}I pulmonary uptake (254). If pulmonary fibrosis is suspected, then appropriate periodic pulmonary function testing and consultation should be obtained. The presence of pulmonary fibrosis may limit the ability to further treat metastatic disease with radioiodine.

R58. Pulmonary micrometastases should be treated with radioiodine therapy, repeated every 6–12 months as long as disease continues to respond, as the highest rates of complete remission are reported in these subgroups (243,248,255)—Recommendation A

R59. The selection of radioiodine activity to administer for pulmonary micrometastases can be empiric (100–300 mCi)

or estimated by dosimetry to limit whole body retention to 80 mCi at 48 hours and 200 cGy to the red bone marrow—Recommendation C

Macronodular pulmonary metastases may also be treated with radioiodine if demonstrated to be iodine avid. How many doses of radioiodine to give and how often to give it is a decision that must be individualized based on the disease response to treatment, the rate of disease progression in between treatments, age of the patient, size of the lesion, and presence/absence of other metastatic lesions and the availability of other treatment options including clinical trials (243,248)

R60. Radioiodine-avid macronodular metastases should be treated with radioiodine, and treatment repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing thyroglobulin), but complete remission is not common and survival remains poor. The selection of radioiodine activity to administer can be made empirically (100–300 mCi) or estimated by dosimetry to limit whole body retention to 80 mCi at 48 hours and 200 cGy to the red bone marrow—Recommendation B

Nonradioiodine avid pulmonary disease. In one study, administration of 200–300 mCi of radioiodine to 10 patients with pulmonary macrometastases who had negative 3 mCi diagnostic scans was associated with a fivefold increase in the median TSH-suppressed thyroglobulin, and death was reported in several patients within 4 years of treatment (256). Although not specifically limited to pulmonary lesions, patients with increasing volumes of 18-fluorodeoxyglucose (FDG)-avid disease seen on positron-emission tomograpy (PET) scans were less likely to respond to radioiodine and more likely to die during a 3-year follow-up compared with FDG-negative patients (257). One study found that radioiodine therapy of metastatic lesions that were positive on FDG-PET scanning was of no benefit (258). In other studies of FDG-PET imaging, however, insufficient details exist in patients known to have pulmonary metastases to assess the utility of this modality to predict treatment response or prognosis (259). Traditional cytotoxic chemotherapeutic agents such as doxorubicin and cisplatin, are generally associated with no more than 25% partial response rates, and complete remission has been rare (260).

R61. Evidence of benefit of routine treatment of nonradioiodine avid pulmonary metastases is insufficient to recommend any specific systemic therapy—Recommendation I

R62. For many patients, metastatic disease is slowly progressive and patients can often be followed conservatively on TSH-suppressive therapy with minimal evidence of radiographic or symptomatic progression. For selected patients, however, other treatment options need to be considered, such as metastasectomy, endobronchial laser ablation, or external beam radiation for palliation of symptomatic intrathoracic lesions (e.g., obstructing or bleeding endobronchial masses), and pleural or pericardial drainage for symptomatic effusions. Referral for participation in clinical trials should be considered—Recommendation C

Treatment of bone metastases. In the management of the patient with bone metastases, key criteria for therapeutic decisions include risk for pathologic fracture, particularly in a weight-bearing structure; risk for neurologic compromise from vertebral lesions; presence of pain; avidity of radioiodine uptake; and potential significant marrow exposure from radiation arising from radioiodine-avid pelvic metastases.

R63. Complete surgical resection of isolated symptomatic metastases has been associated with improved survival and should be considered, especially in patients less than 45 years old (212,246)—Recommendation B

R64. Radioiodine therapy of iodine-avid bone metastases has been associated with improved survival and should be used (212,248). The radioiodine activity administered can be given empirically (150–300 mCi) or estimated by dosimetry (140)—Recommendation B

R65. When skeletal metastatic lesions arise in locations where acute swelling may produce severe pain, fracture, or neurologic complications, external radiation and the concomitant use of glucocorticoids to minimize potential TSH-induced and/or radiation related tumor expansion should be strongly considered (261)—Recommendation C

R66. Painful lesions that cannot be resected can also be treated by several options individually or in combination, including: radioiodine, external beam radiotherapy; intra-arterial embolization (215,262), radiofrequency ablation (263), periodic pamidronate or zoledronate infusions (with monitoring for development of possible osteonecrosis) (252), or bone-seeking radiopharmaceuticals such as strontium-89 or samarium-153 (264). While many of these modalities have been shown to relieve bone pain in cancer, they have not necessarily been reported to have been used in patients with thyroid cancer—Recommendation C

R67. Evidence is insufficient to recommend treatment of asymptomatic, non-radioiodine responsive, stable lesions that do not threaten nearby critical structures—Recommendation I

Treatment of brain metastases. Brain metastases typically occur in older patients with more advanced disease at presentation, and are associated with a poor prognosis (237). Surgical resection and external beam radiotherapy traditionally have been the mainstays of therapy (237,265). There are few data showing efficacy of radioiodine.

R68. Complete surgical resection of central nervous system (CNS) metastases should be considered regardless of radioiodine avidity, as it is associated with significantly longer survival—Recommendation B

R69. CNS lesions that are not amenable to surgery should be considered for external beam irradiation. Often very targeted approaches (such as radiosurgery) are employed to limit the radiation exposure of the surrounding brain tissue. Whole-brain and spine irradiation could be considered if multiple metastases are present—Recommendation C

R70. If CNS metastases do concentrate radioiodine, then radioiodine could be considered. If radioiodine is being considered, prior external beam radiotherapy and concomitant glucocorticoid therapy are strongly recommended to minimize the effects of a potential TSH-induced increase in tumor size and the subsequent inflammatory effects of the radioiodine (261)—Recommendation C

Management of complications of radioiodine therapy. While radioiodine appears to be a reasonably safe therapy, it is associated with a cumulative dose-related low risk of early and late onset complications such as salivary gland damage, nasolacrimal duct obstruction (268), and secondary malignancies (267). Therefore, it is important to ensure that the benefits of repeated radioiodine therapy outweigh the potential risks. There is probably no dose of radioactive iodine that is completely safe nor is there any maximum cumulative dose that could not be used in selected situations. However, with higher individual and cumulative doses there are increased risks of side effects as discussed previously.

R71. For acute transient loss of taste or change in taste and sialadenitis, some have recommended measures to prevent damage to the salivary glands including amifostine, hydration, sour candies and cholinergic agents (268), but evidence is insufficient to recommend for or against these modalities. One recent study suggested sour candy may actually increase salivary gland damage when given within 1 hour of radioiodine therapy, compared to its use until 24 hours post-therapy (269). For chronic salivary gland complications, such as dry mouth and dental caries, cholinergic agents may increase salivary flow (268)—Recommendation I

R72. Patients with xerostomia are at increased risk of dental caries and should discuss preventative strategies with their dentists—Recommendation C

R73. Surgical correction should be considered for nasolacrimal outflow obstruction, which often presents as excessive tearing (epiphora) but also predisposes to infection—Recommendation B

Second malignancies and leukemia from radioiodine therapy. Long-term follow-up studies demonstrate a very low risk of secondary malignancies (bone and soft tissue malignancies, colorectal cancer, salivary tumors, and leukemia) in long-term survivors (267). The risk of secondary malignancies is dose-related (267). There appears to be an increased risk of breast cancer in women with thyroid cancer (270). It is unclear whether this is the result of screening bias, radioiodine therapy, or other factors.

R74. Because there is no evidence demonstrating a benefit of more intensive screening, all patients with thyroid cancer should be encouraged to seek age-appropriate screenings for cancer according to routine health maintenance recommendations—Recommendation C

Other risks to the bone marrow from radioiodine therapy. Published data indicate that when administered activities are selected to remain below 200 cGy to the bone marrow, minimal transient effects are noted in white blood cell (WBC) and platelet counts (254). However, persistent mild decrements in white blood count and/or platelets are not uncommon in patients who have received multiple radioiodine therapies. Furthermore, radiation to the bone marrow is impacted by several factors, including renal function.

R75. Patients receiving therapeutic doses of radioiodine should have baseline complete blood cell (CBC), platelet count and assessment of renal function—Recommendation C

Effects of radioiodine on gonadal function and in breast-feeding women. Gonadal tissue is exposed to radiation from radioiodine in the blood, urine and feces. Temporary amenorrhea/oligomenorrhea lasting 4–10 months occurs in 20%–27% of menstruating women after ^{131}I therapy for thyroid cancer. Although the numbers of patients studied are small, long-term rates of infertility, miscarriage, and fetal malformation do not appear to be elevated in women after radioiodine therapy (271,272). One large retrospective study suggested that pregnancy should be postponed for 1 year after therapy because of an increase in miscarriage rate (273). Ovarian damage from radioiodine therapy may result in menopause occurring approximately 1 year earlier than the general population, but this result was not associated with cumulative dose administered or the age at which the therapy was given (274). In men, radioiodine therapy may be associated with a temporary reduction in sperm counts and elevated serum follicle-stimulating hormone (FSH) levels (275,276). Higher cumulative doses (500–800 mCi) in men are associated with an increased risk of persistent elevation of serum FSH levels, but fertility and risks of miscarriage or congenital abnormalities in subsequent pregnancies are not changed with moderate radioiodine doses (approximately 200 mCi) (277,278). Permanent male infertility is unlikely with a single ablative dose of radioiodine, but theoretically there could be cumulative damage with multiple treatments. It has been suggested that sperm banking be considered in men who may receive cumulative radioiodine doses 400 mCi or more (278). Gonadal radiation exposure is reduced with good hydration, frequent micturition to empty the bladder and avoidance of constipation (279).

R76. Women receiving radioactive iodine therapy should avoid pregnancy for 6–12 months—Recommendation B

R77. Radioactive iodine should not be given to breast-feeding women. Depending on the clinical situation, radioiodine therapy could be deferred until a time when lactating women have stopped breast-feeding for at least 6–8 weeks. Dopaminergic agents might be useful in decreasing breast exposure, although caution should be exercised given the risk of serious side-effects associated with their routine use to suppress postpartum lactation—Recommendation B

How should thyroglobulin-positive patients be managed?

If the unstimulated thyroglobulin is or becomes detectable or stimulated thyroglobulin levels rise to greater than 2 ng/mL, imaging of the neck and chest should be performed to search for metastatic disease, typically with neck ultrasound and with thin-cut (5–7 mm) helical chest CT. Iodinated contrast should be avoided if radioiodine therapy is planned within the subsequent few months, although intravenous contrast may aid

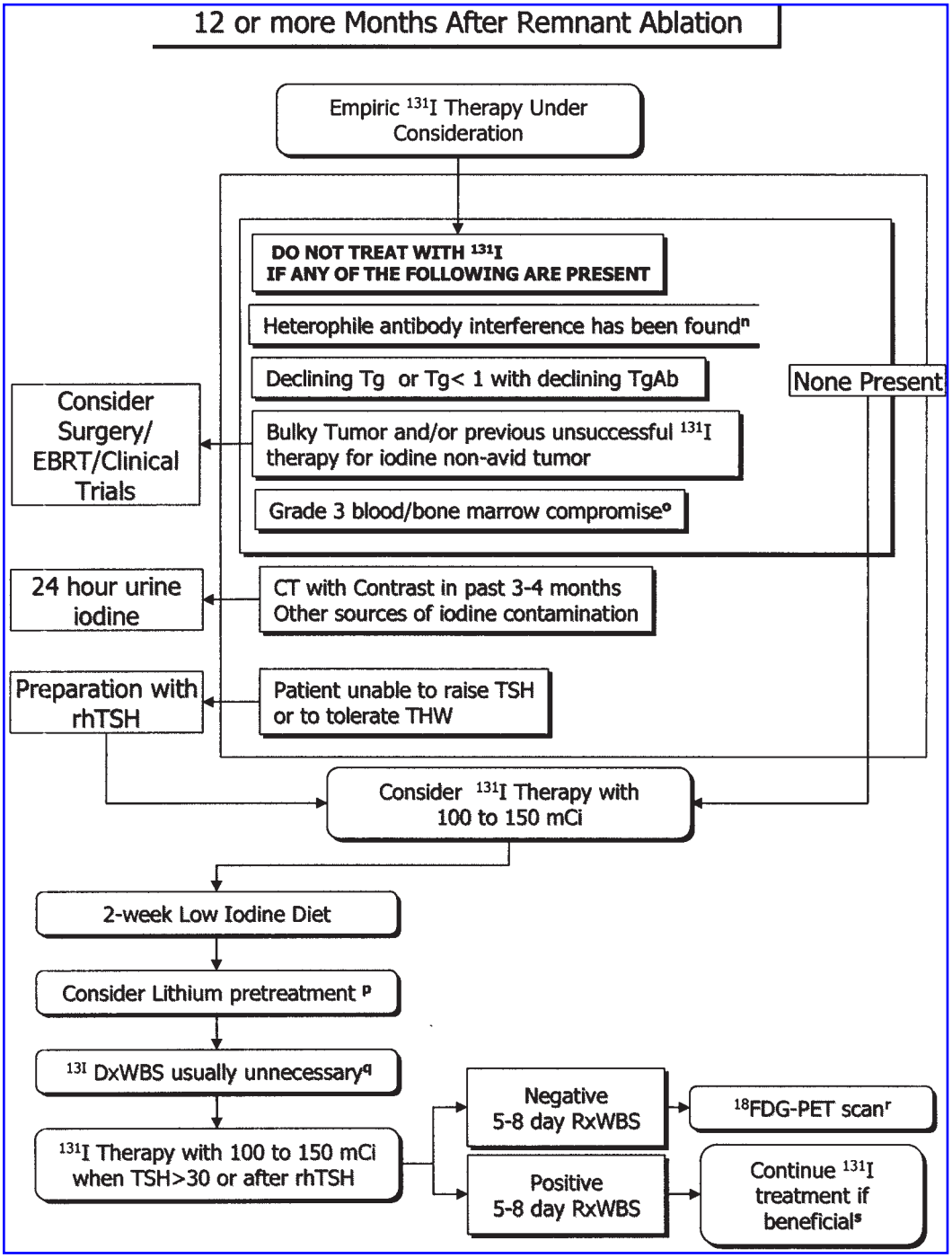

FIG. 4. Considerations for empiric treatment with radioiodine. [n]Thyroglobulin (Tg) that rises with thyrotropin (TSH) stimulation and falls with TSH suppression is unlikely to result from heterophile antibodies. [o]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0, (www.ctep.cancer.gov). [p]Lithium may be beneficial at this point but there are few clinical studies. [q]DxWBS is diagnostic whole-body scintigraphy. [r]FDG-PET scanning sensitivity and specificity may be enhanced with stimulation (rhTSH or THW) and by fusion with CT imaging (PET/CT). [s]Dosimetry could be considered to allow administration of maximum radioiodine activity if the tumor is life-threatening. (Reprinted with permission from J Nucl Med 46:1079–1088, 2005.)

in identification of mediastinal disease. If imaging is negative for disease that is potentially curable by surgery, then empiric therapy with radioiodine (100–200 mCi) should be considered to aid localization or for therapy of surgically incurable disease (Fig. 4). This approach may identify the location of persistent disease in approximately 50% of patients (203,280) with a wide range of reported success. Some investigators have reported a decrease in serum thyroglobulin after empiric radioiodine therapy in patients with negative RxWBS (281,282), but there is no evidence for improved survival with empiric therapy in this setting (258,283). On the other hand, serum thyroglobulin levels may decline without specific therapy (282).

A cutoff value of thyroglobulin above which a patient should be treated with an empiric dose of radioiodine is difficult to determine, in part because of the wide variation in available thyroglobulin assays (including those used in reports suggesting benefit of such therapy) and the differences in thyroglobulin levels based on method and degree of TSH stimulation or suppression. Recent studies have reported primarily on patients with thyroglobulin levels after thyroxine withdrawal of 10 ng/mL or higher, and it has been suggested that a corresponding level after rTSH stimulation would be 5 ng/mL (204,256,280,282,283). A thyroglobulin level that is rising may warrant greater concern for the need for empiric therapy, although data regarding the appropriate rate of change are minimal (202).

R78. Empiric radioactive iodine therapy (100–200 mCi) might be considered in patients with elevated or rising serum thyroglobulin levels in whom imaging has failed to reveal a potential tumor source—Recommendation C

R79. If persistent nonresectable disease is localized after an empiric dose of radioiodine, and there is objective evidence of significant tumor reduction, then radioiodine therapy should be repeated until the tumor has been eradicated or the tumor no longer responds to treatment. The risk of repeated therapeutic does of radioiodine must be balanced against uncertain long-term benefits—Recommendation C

Patients with a negative posttreatment whole-body scan (RxWBS)

R80. If an empiric dose (100–200 mCi) of radioiodine fails to localize the persistent disease, ^{18}FDG-PET scanning should be considered, especially in patients with unstimulated serum thyroglobulin levels more than 10–20 ng/ml, in order to localize metastatic lesions that may require treatment or continued close observation (284,285)—Recommendation B

Stimulation with endogenous TSH after thyroxine withdrawal or rhTSH (286) and CT fusion (287) may enhance the sensitivity and specificity of FDG-PET scanning.

R81. Thyroglobulin positive, RxWBS-negative patients with disease that is incurable with surgery and is structurally evident or visualized on FDG-PET scan can be managed with thyroid hormone suppression therapy, external beam radiotherapy, chemotherapy, radiofrequency ablation, chemoembolization, or monitoring without additional therapy if stable. Clinical trials should also be considered—Recommendation C

R82. Thyroglobulin-positive, RxWBS-negative patients with no structural evidence of disease can be followed with serial structural imaging studies and serial thyroglobulin measurements, with both performed more frequently if the thyroglobulin level is rising. When and how often to repeat FDG-PET imaging in this setting is less certain—Recommendation C

What is the role of external beam radiotherapy in treatment of metastatic disease?

R83. External beam radiation should be used in the management of unresectable gross residual cervical disease, painful bone metastases, metastatic lesions in critical locations likely to result in fracture, neurological, or compressive symptoms that are not amenable to surgery (e.g., vertebral metastases, CNS metastases, selected mediastinal or subcarinal lymph nodes, pelvic metastases) (174,226)—Recommendation B

What is the role of chemotherapy in the treatment of metastatic disease?

Studies of chemotherapy for advanced, radioiodine-resistant differentiated thyroid carcinoma are limited. Doxorubicin monotherapy may be effective in up to 40% of patients (most partial response or stable disease) when dosed appropriately (60–75 mg/m^2 every 3 weeks) (288–291) but durable responses are uncommon. Most studies of combination chemotherapy show no increased response over single agent doxorubicin and increased toxicity (292). Some specialists recommend consideration of single agent doxorubicin or paclitaxel, or a combination of these agents based on limited data in anaplastic thyroid carcinoma (293). One recent study evaluated the effect of combination chemotherapy (carboplatinum and epirubicin) under TSH stimulation (endogenous or rhTSH) (294), demonstrating an overall rate of complete and partial response of 37%. These data need to be confirmed prior to consideration for general use.

R84. Chemotherapy has modest benefit in patients with advanced, radioiodine-resistant thyroid cancer. Patients with progressive disease should first be considered for clinical trials. If clinical trials are unavailable or the patient prefers standard cytotoxic chemotherapy, doxorubicin used as a single agent or in combination with other agents may be considered—Recommendation C

Should patients skip chemotherapy and instead opt for clinical trials?

If the patient qualifies for a clinical trial, they should consider bypassing traditional chemotherapy and moving directly to clinical trials. However, patients often cannot participate in clinical trials because of the time and expense required, or failure to meet strict eligibility criteria. Most available trials can be found listed at www.clinicaltrials.gov; www.nci.nih.gov; www.centerwatch.com; or www.thyroid.org

R85. Patients with advanced, progressive, unresectable radioiodine non-responsive thyroid cancer who are being considered for chemotherapy should be considered for entry into clinical trials—Recommendation C

What Are the Directions for Future Research?

Novel therapies and clinical trials

While surgery and the judicious use of radioactive iodine, as described in these guidelines, is sufficient treatment for the majority of patients with differentiated thyroid cancer, a minority of these patients experiences progressive, life-threatening growth and metastatic spread of the disease. For these individuals, experimental treatments may be considered. Several clinical trials are already in progress; others are at various stages of development and the number of available clinical trials is likely to grow rapidly. The recent ex-

plosion of knowledge regarding the molecular and cellular pathogenesis of cancer has led to the development of a range of targeted therapies, now beginning clinical evaluation. These therapies can be grouped into a number of categories:

Oncogene inhibitors. Tyrosine kinase inhibitors target the activated RET/PTC oncogene, responsible for a proportion of PTC. Inhibitors of RAS, RAF, and MEK kinase target various members of the same signaling pathway. Several of these agents are in development, with at least one clinical trial underway. Specific oncogene targeting for follicular thyroid cancer and Hürthle thyroid cancer awaits better understanding of the pathways involved in initiation of these tumor types.

Modulators of growth or apoptosis. Key components of growth and apoptotic pathways are targeted by PPARγ activators, including COX2 inhibitors; retinoids, which activate PPARγ/RXR heterodimers; Bortezomib (Velcade®, Millenium Pharmaceuticals, Cambridge, MA), which inactivates the cancer proteasome; and derivatives of geldanomycin, which target the hsp-90 protein. Clinical trials in thyroid cancer of each of these agents are available.

Angiogenesis inhibitors. Targeting of vascular endothelial growth factor (VEGF) and other members of the signaling cascade responsible for neoangiogenesis may limit the growth of cancers by restricting their blood supply. Trials of several of these agents are currently underway in both anaplastic and differentiated thyroid cancer.

Immunomodulators. Stimulation of the immune response to cancer may be achieved by augmenting the activity of antigen-presenting dendritic cells. This approach has shown possible benefits in phase 1 clinical trials, but has not yet been studied in thyroid cancer. The apparent immunogenicity of thyroid cells makes this an attractive approach for future clinical trials.

Gene therapy. Preclinical studies have demonstrated some efficacy in thyroid cancer cell lines. Approaches include introducing toxic genes under the control of thyroid-specific promoters, or restoration of the p53 tumor-suppressor gene in anaplastic thyroid cancer cell lines. Problems with gene delivery limit the clinical utility of these approaches, which have not yet reached clinical trials in thyroid cancer.

Each of these targeted approaches holds promise for our future ability treat patients with life-threatening disease unresponsive to traditional therapy. In the meantime, for appropriate patients, entry into one of the available clinical trials may be an attractive option.

Better understanding of the long term-risks of radioiodine

With the more widespread use of radioactive iodine in the management of thyroid cancer, it is imperative that we have a better understanding of the long-term risks associated with its use. Research that focuses on how to minimize the impact of radioiodine on the salivary glands in order to prevent siladenitis and xerostomia would provide a significant benefit to patients. A better understanding of the long-term effects of radioiodine on reproductive issues in men and women is also an important topic. Finally, while the risk of second malignancies appears small following the usual doses of radioiodine used for remnant ablation, we need better understanding of the long-term risks for salivary gland tumors, gastrointestinal tumors, bladder tumors, and colon cancers when repeated doses of radioiodine are needed in young patients with potentially curable thyroid cancer.

Clinical significance of persistent low-level thyroglobulin

After initial surgery and radioiodine therapy some patients will have persistently detectable stimulated serum thyroglobulin when evaluated 9–12 months later. Most of these patients have stimulated thyroglobulin levels in the range of 1–10 ng/mL, levels typically associated with a small volume of tissue. Some of these patients demonstrate a subsequent spontaneous fall in thyroglobulin over time, others remain stable, while still others demonstrate rising thyroglobulin levels. The optimal management of these patients is unknown. How often should they undergo neck ultrasound or stimulated serum thyroglobulin testing? Which (if any) of these patients undergo chest CT, PET, or empiric radioiodine therapy? Can we improve our abilities to predict and monitor which patients are likely to be harmed by their disease as opposed to those who will live unaffected by theirs? Does metastatic disease in small local lymph nodes have the potential to metastasize to distant sites during observation while on TSH-suppression therapy? The current impetus to test and treat all of these patients is based on the argument that early diagnosis may lead to early treatment of residual disease when treatment is more likely to be effective, as opposed to less effective treatment when the tumor is more bulky, more extensive, or spread to inoperable locations. However, there is no current proof that aggressive treatment of minimal residual disease improves patient outcome. This is brought into focus by the fact that only about 5% of PTC patients die of their disease, yet more than one third of PTC patients are likely to have persistent disease based on persistent measurable thyroglobulin to stimulation testing.

The problem of thyroglobulin antibodies

Antithyroglobulin antibodies are a common clinical problem in patients with differentiated thyroid carcinoma (20%) (198). The presence of these antibodies usually interferes with serum thyroglobulin measurement and recovery assays do not appear to accurately predict this interference (198,295). Decreasing antibody levels are correlated with "disease-free" status while increasing levels suggest persistent disease (199,296). Measurement of thyroglobulin mRNA in the blood may be a sensitive marker for persistent thyroid cells even in the presence of anti-thyroglobulin antibodies (297–299), but RNA extraction is not well standardized and some studies question the specificity of this marker (300,301). Future studies optimizing thyroglobulin mRNA measurements in blood from DTC patients with antithyroglobulin antibodies, further development of thyroglobulin assays that have limited interference by antithyroglobulin antibodies or methods to clear antithyroglobulin antibodies prior to thyroglobulin measurement are needed to better monitor this challenging subgroup of patients with DTC.

Small cervical lymph node metastases

The rates of cervical lymph node metastases generally range from about 20%–50% in most large series of differen-

tiated thyroid carcinoma, with higher rates in children or when mircometastases are considered. The location and number of lymph node metastases is often difficult to identify at before or at the time of surgery, especially micrometastases. Although postoperative ^{131}I given to ablate the thyroid remnant undoubtedly destroys some micrometastases, the most common site of recurrence is in cervical lymph nodes, which comprises the majority of all recurrences. Future research must be directed to developing techniques to identify small cervical metastases, which in a substantial number of cases progress to overt, clinically significant metastases.

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November 16, 2005

Terry Davies, MD
Editor-in-Chief
THYROID

Dear Dr. Davies:

I am writing this letter to accompany the submission of the manuscript "MANAGEMENT GUIDELINES FOR PATIENTS WITH THYROID NODULES AND DIFFERENTIATED THYROID CANCER" under evaluation for publication in THYROID. Dr. David Cooper, the corresponding author, is acting on behalf of the officers and council of the American Thyroid Association who have reviewed and approved of these guidelines as an official position of our organization. Dr. Cooper will coordinate any necessary clarifications or revisions of these guidelines on behalf of the ATA.

Thank you for considering these guidelines for publication.

Regards,

Ernest L. Mazzaferri, MD
President
American Thyroid Association

Gregory A. Brent, MD
Secretary
American Thyroid Association

Cc: Barbara Smith, Executive Director, American Thyroid Association

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