Evaluation and Treatment of Thyroid Nodules: A Clinical Guide

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ABSTRACT

Thyroid nodules are inexplicably frequent and affect approximately one-third of the adult population. The appropriate clinical management is focused primarily on excluding thyroid cancer and also on evaluating thyroid dysfunction and mechanical obstruction. There remains no evidence that a benign thyroid nodule, once diagnosed appropriately, will progress to a malignant lesion. The initial evaluation should include a complete clinical review, a thyroid sono-gram by an experienced sonographer, a laboratory assessment of thyroid function, and, where indicated, a cytological assessment of the nodule(s) by fine needle aspiration under ultrasound guidance. Only patients with suppressed serum thyroid-stimulating hormone levels, indicating hyperthyroidism, may need further evaluation by radioactive iodine uptake and scanning. Optimal treatment depends on the patient as well as the nodule characteristics. The usual options remain a simple annual follow-up to detect changes in nodule size and thyroid function and surgical removal. Levothyroxine therapy is now seldom indicated because of poor efficacy in nodule suppression and its inability to differentiate benign lesions from thyroid carcinoma. Clinical guidelines have a very arbitrary recommendation of aspiration biopsy in all lesions greater than 1 cm in size, but this proposal has no scientific basis and should always be viewed in the clinical context.

Key Words: benign, diagnosis, malignant, management, multinodular, nodules, thyroid, treatment.

Thyroid nodules (TNs) are among the leading causes of referring patients to an endocrinologist. Indeed, by the time we reach 80 years of age, almost 80% of us have 1 or more such nodules.1 Hence, the neck check has been introduced (Figure 1).2 Usually in clinical practice, when a patient notices a lump in his neck, his principal concern is the possibility of malignancy. However, the vast majority of such lesions are benign, and the patient simply requires periodic follow-up after a careful study of his nodule’s characteristics. Many clinicians are used to considering such nodules as hot or cold, but this type of thinking no longer applies. First, all nodules take up radioiodine, and rarely are they truly cold; second, the activity of a nodule or nodules is better assessed by the patient's serum thyroid-stimulating hormone (TSH) level, which is exquisitely sensitive to thyroid hormone output.

TNs may be single, multiple, cystic, or solid and may or may not be functional. Furthermore, they may be found in the presence of unrelated thyroid dysfunction (eg, secondary to inflammation). Accordingly, both the thyroid functional status and pathological evaluation need to be assessed. In addition, there is a wide spectrum of TNs, ranging from small incidentalomas to bothersome, symptomatic, large neck masses.

NOMENCLATURE

A wide variety of terms are used in discussions of TNs. Benign and malignant are self-explanatory. Hot refers to positive uptake of radioiodine on scanning, whereas cold is the old term suggesting a reduced uptake of radioiodine. Some people even use the...
Fig 1. The thyroid neck check. All you need is a glass of water and a handheld mirror. Hold the mirror, focusing on your neck just between the Adam’s apple and the collarbone, where your thyroid is located. While focusing on this area, tip your head back, take a drink of water, and swallow. As you swallow, look at your neck. Check for any bulges or enlargement in this area while you swallow. Do not confuse the Adam’s apple with the thyroid gland. Reprinted with permission from http://www.thyroidawareness.com. Copyright 2008, American Association of Clinical Endocrinologists. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

term warm for an in-between result. Cystic refers to the accumulation of fluid seen on ultrasound (US), whereas complex refers to a lesion with both solid and cystic components. Multinodular goiter is usually used when there are more than 2 nodules, whereas the term colloid goiter is now used by pathologists only to express the presence of colloid formation in a benign follicular lesion.

**EPIDEMIOLOGY**

The prevalence of TNs by physical examination is around 5% to 10% of the population, but physical examination of the thyroid gland has proven to be remarkably inaccurate with the introduction of thyroid sonography. This has caused most thyroidologists to perform their own thyroid sonographic examinations, and some of us believe that a real-time US examination is an essential part of all thyroid patient evaluations. Indeed, US can discover TNs in 20% to 60% of the population, TNs being more frequent in women and the elderly (Figure 2). The old fashioned evaluation by radioiodine scanning showed that 5% to 10% of palpated TNs were hot, whereas approximately 85% were cold, but data from US series show a much lower frequency of active nodules. Nevertheless, a significant proportion of patients with multinodular thyroid disease have suppressed TSH levels and active nodules. The active single nodule, however, remains relatively uncommon.

**FREQUENCY OF MALIGNANCY**

The risk of a TN being thyroid cancer is between 1% and 10%. It was once thought to be better to have more than 1 TN, but the prevalence of cancer is similar between solitary and multinodular goiters. Usually, cancers take up less radioiodine than normal thyroid tissue and are called cold nodules on scintigraphy, but this does not mean that cold nodule is synonymous with malignancy because the vast majority of cold nodules are benign. Hence, routine thyroid scanning is a quite useless and expensive evaluation.

Fig 2. Prevalence of palpable thyroid nodules detected at autopsy or by ultrasonography (solid circles) or by palpation (open squares) in subjects without radiation exposure or known thyroid disease. Reprinted with permission from the New England Journal of Medicine. Copyright 1993, Massachusetts Medical Society.
ETIOLOGY AND NATURAL HISTORY

Many environmental and constitutional factors have been related to the increased risk of developing TNs (Table 1).

The first step in the transformation of the thyroid epithelial cell from the normal state to an abnormal state follows the generation of cellular hyperplasia. This may be induced by random somatic mutations or rearrangements in genes that encode mitogen-activated protein kinase pathway effectors, the TSH receptor, or a G-protein, or this may follow a goitrogenic stimulus such as excessive TSH stimulation (Figure 3). This induction of growth exacerbates cellular mutagenesis with the formation of mutated cellular clones that generate the nodules. When the mutation results in an active TSH receptor, the resulting nodule is autonomous, and the patient may develop hyperthyroidism and a suppressed TSH.

The evolution and natural history of TNs are variable and unpredictable. Some TNs will continue growing, and some will grow to a great extent and cause tracheal obstruction, whereas others will diminish with time, perhaps following infarction and hemorrhage. Hence, solid nodules tend to persist, and cystic lesions sometimes spontaneously disappear. As more nodules develop, the chance of an autonomous nodule being among them increases, and so a toxic multinodular goiter develops, most commonly in the elderly. Such TN activity may vary in time, and some autonomous lesions may evolve to cause changes in total thyroid function only after exposure to iodine; this is seen commonly after computed tomography (CT) scanning with iodine-containing contrast material. The iodine load allows the production of thyroid hormones more efficiently than before. Such development of autonomous nodules has been reported to occur in approximately 5% of cases.

CLINICAL MANAGEMENT

In the study of TNs, clinicians must always be aware of the possibility of thyroid cancer, and certain clinical, analytical, US, and cytological data raise the suspicion of malignancy, but on their own, they may not prove it. However, the presence of these risk factors indicates a higher chance of malignancy.

Recent American and European guidelines recommend performing a complete evaluation only of those nodules that are larger than 1 cm. However, the rationale for this recommendation is bewildering. A malignant nodule starts its evolution as a single malignant cell. In theory, some of these malignant cells may have evolved from a previously benign abnormal cell within a TN, but the malignant transformation may also have started from a normal thyroid epithelial cell or from a thyroid stem cell. Therefore, the malignant TNs will have been smaller than 1 cm, and a small nodule does not guarantee benignity or low risk. In fact, some studies have calculated that the risk of malignancy in TNs less than 1 cm in size is as much as 10%. Of even more concern is the finding that 70% of these patients with small malignant nodules may have positive local lymph nodes.

Office Evaluation

History

Normally functioning TNs are usually asymptomatic and are generally detected by routine neck examination (Figure 4). At presentation, the patient may complain of the presence of a slowly growing lump in the neck. TNs are rarely painful unless there has been an acute hemorrhage. Occasionally, TNs produce difficulty in swallowing that may indicate rapid growth, which is characteristic of malignancy. More often, it is vague discomfort on swallowing. The existence of a family history of benign TNs is common, and familial thyroid cancer is well described. A moderate risk factor for malignancy is an age below 20 years and greater than 45 years, and male gender is also a factor, whereas a highly suspicious indicator of malignancy includes a history of head and neck radiation.

![Image](image-url)
Examination

Observations of importance include several physical signs, rapid tumor growth (although thyroid cancers usually grow slowly), regional lymphadenopathy, and suspicion of distant metastases. If none of these factors are present, the clinical suspicion for malignancy is low (Table 2).

Laboratory Examination

Thyroid Function Tests

The first study that should be performed in any patient with TNs is the determination of serum TSH to distinguish the autonomous nodules from the nonautonomous nodules. A low serum TSH level usually means hyperthyroidism secondary to an autonomous nodule, and the patient should be managed accordingly. In this setting, the next step is to obtain a sonogram and a radioiodine thyroid scan. If the thyroid scan shows that the TN concentrates a great deal of radioactivity, then no additional cytologic evaluation is necessary because functioning TNs are very rarely malignant. However, it is also possible that the cause of the increased thyroid activity is not the nodule or nodules but rather coincidental Graves’ disease. Graves’ disease may present with multinodularity and can be confirmed by the presence of serum TSH receptor antibodies. There is no evidence that Graves’ disease itself leads to multinodularity, but such a presentation is more likely the reflection of 2 common disorders. The sonogram may also reveal that the palpated nodule and the active nodule are not coincidental.

TSH levels in TN patients are usually within the normal range. A high TSH indicates hypothyroidism, and measurement of thyroid antibodies is advisable in this situation to confirm coincidental Hashimoto’s thyroiditis. There is an increased risk of thyroid cancer in patients with autoimmune thyroid disease. Interestingly, serum TSH concentrations may have an auxiliary value in raising suspicion of malignancy, as suggested by a recent study in which the risk of malignancy in a TN increased proportionately with serum TSH levels.

Tumor Markers

Thyroglobulin is one of the most useful tumor markers for thyroid cancer recurrence once a patient has had his thyroid removed and any remaining tissue ablated with radioiodine. However, the determination of serum thyroglobulin has no value in the initial study of patients with TNs. All thyroid diseases may cause an increased serum thyroglobulin so that it...
has no value as a routine thyroid function test. In contrast, a controversy exists about the usefulness of determining plasma calcitonin, oversecreted by medullary thyroid cancer cells, as part of the routine evaluation of TNs. The prevalence of medullary thyroid cancer in TNs ranges from 0.3% to 1.3%, and this makes such testing highly cost-ineffective. Several European prospective studies of unselected TNs have demonstrated that regular measurement of serum calcitonin allows the detection of unsuspected medullary thyroid carcinoma with a frequency of 1 in 200 to 300 TNs, which gives a better sensitivity than fine needle aspiration (FNA). Therefore, some authors have recommended routine calcitonin screening to improve the TN outcome. However, in addition to the cost, the sensitivity and specificity of this practice have not been clearly determined.

Thyroid Autoantibodies
The measurement of thyroid autoantibodies is not needed in euthyroid patients with TNs but is recommended in the presence of thyroid dysfunction. It is worth noting, however, that the presence of antibodies to thyroid peroxidase and thyroglobulin, which correlate with an intrathyroidal lymphocytic reaction, may confer an improved prognosis in patients with thyroid cancer.
Table 2. Indicators of Possible Malignancy.

<table>
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<tr>
<th>Clinical Indicators</th>
<th>Physical Signs</th>
<th>Sonographic Indicators</th>
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<tr>
<td>Past family history of thyroid cancer (especially in medullary cancer)</td>
<td>Hard consistency</td>
<td>Intranodular microcalcification</td>
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<td>History of head and neck radiation</td>
<td>Fixation to surrounding structures</td>
<td>Intranodular hypervascularity (evaluated by Doppler)</td>
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<tr>
<td>Rapid tumor growth</td>
<td>Hoarseness (vocal cord palsy)</td>
<td>Hypoechogeticity</td>
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<td></td>
<td>Regional lymphadenopathy</td>
<td>Nodule with irregular borders</td>
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<td></td>
<td>Compressive symptoms</td>
<td>Absence of peripheral halo</td>
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<tr>
<td></td>
<td>(dysphagia, dyspnea, or coughing)</td>
<td>Presence of regional lymphadenopathy</td>
</tr>
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<td></td>
<td>Large nodules (&gt;4 cm)</td>
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US Examination

Initial Evaluation
Thyroid US is the most accurate imaging technique for the detection of TNs, and this procedure is mandatory when a nodule is discovered at palpation or by any other method (eg, CT or magnetic resonance (MRI)). It is important to know the nodule size, the number of nodules (presence of additional nonpalpable nodules), and their location and characteristics. In addition, US exploration is useful for detection of suspicious lymph nodes, which is important in the assessment of malignancy. Furthermore, US has the advantage of being a well-tolerated innocuous technique with low cost and no irradiation of the patient. The main drawbacks of thyroid US are the dependence on the operator's experience and the difficulty in viewing low retrosternal goiters, which may require CT/MRI evaluation.

Diagnostic Accuracy
The sonogram can help not only in the diagnosis of TNs but also in the evaluation of the nodules. However, US features of malignancy are not highly reliable when applied to the individual patient and simply add to the constellation of risk factors available for the clinician to consider. US characteristics suggestive of malignancy are summarized in Table 2. A combination of these findings may be highly predictive for malignancy. Although such sonographic characteristics are superior to just nodule size for identifying malignancy, a rapid increase in size is also an important risk factor.

Other Imaging Techniques

Scintigraphy
This has been the imaging technique of choice to evaluate the functional activity of the thyroid gland and the TN in hyperthyroid states. As already mentioned, routine thyroid scintigraphy with radioactive iodine (RAI) or technetium is not helpful in the evaluation of euthyroid or hypothyroid patients with TNs. Scintigraphy uses ionized radiation; hence, it is contraindicated in pregnancy and lactation.

CT/MRI Scanning
These techniques are particularly useful in the evaluation of retrosternal goiters. They cannot distinguish benign TNs from malignant ones and are not as helpful as US in distinguishing benign lymph nodes from malignant ones. In TN patients, it is better to use MRI than CT because the high iodine load in the CT contrast medium can precipitate a toxic nodular goiter. This is not a problem with MRI contrast media.

Positron Emission Tomography
Positron emission tomography evaluations are highly informative for thyroid functionality but have no advantage over other scanning procedures in the routine evaluation of TNs. A recent study showed that fluorodeoxyglucose metabolic activity did not significantly differ between malignant and benign follicular neoplasias.

FNA

Indications
The general recommendation is that nodules greater than 1 cm in size should be biopsied. This of course makes no biological sense because even carcinomas start small. However, as a practical approach, this may be appropriate, but any fast growing lesion and any lesion with suspicious US characteristics should be aspirated. Patients with suppressed TSH levels should have RAI scanning beforehand because the biopsy of active nodules is not necessary.

Technique
A #27 or #25 needle, mounted in a 10-mL syringe, is passed through the lesion under US control. Negative
pressure is induced and released before withdrawal of the needle so that the aspirate will remain in the needle hub. The aspirate is smeared on a glass slide, fixed, and stained for examination. Complications are rare. The patient may have at the very most some mild discomfort, swelling, and ecchymoses and most commonly has none of these.

Improving the Yield of FNA
US is an excellent aid for improving the accuracy of FNA cytology. US guidance can reduce the rate of inadequate smears from 15% to 3%. Since 2007, all FNA procedures should have been performed with US guidance.

Cytology
For determining whether a TN is malignant or benign, cytological diagnosis is, despite its limitations, still the most accurate and powerful preoperative study and must be included in the initial evaluation of all TNs except the autonomous variety. Unfortunately, cytological reports are frequently confusing. Cytophysical samples should be first divided into adequate and inadequate samples. The term nondiagnostic is ambiguous and should be avoided in cytological reports. Some authors consider adequate only those specimens that include 6 or more groups of 10 to 20 well-preserved follicular cells on at least 2 slides.

Inadequate samples often necessitate a repeat FNA. Data from Mount Sinai in a series of almost 500 cytologic samples showed 43% of such samples to be inadequate specimens. This high percentage is related to the large number of different referring physicians (>50) who perform too few procedures to develop good technique and confirms the importance of a certain degree of skill and experience needed to yield useful data.

Five Categories of Adequate Samples

Benign  This category includes adenomatous nodules, multinodular goiters, cysts, and thyroiditis (Figure 5). Nodules should be periodically observed, and if they are highly suspicious, FNA should be repeated. A recent study showed the result of repeat FNAs in 282 benign nodules. Thirty-five of the initially benign nodules showed features suspicious of malignancy, and 7 (20%) of these suspicious nodules were proven to be malignant at surgery. The authors recommended a minimum of 3 benign FNA studies for complete follow-up; much more than 3 would certainly not seem practical. Indeed, if a clinician is so suspicious of malignancy that he pursues this route, then one could question why surgery was not recommended earlier. The value of repeated FNA in over 10,000 procedures showed that repeating thyroid FNAs on benign cytologically diagnosed nodules improved the accuracy in the diagnosis from 90% to 98%. The authors recommended repeating FNA in 1 year for patients with TNs diagnosed as benign.
Malignant This category encompasses carcinoma (papillary, medullary, and anaplastic), lymphoma, and metastases from another primary cancer. Cytological features of papillary thyroid cancer are straightforward, and generally the diagnosis is not an issue (Table 3 and Figure 5). The recommended procedure for these lesions is, of course, surgical excision.

Follicular Neoplasm Approximately 15% of TNs fall under this category, which covers both benign (adenoma) and malignant (carcinoma) follicular neoplasias. Around 20% of these cases are cancers. Cytology cannot usually distinguish between follicular adenoma and follicular carcinoma, as the cells appear very similar. The pathological difference lies in the presence of vascular or capsular invasion, and this feature can be evaluated only by histological examination of the excised nodule. The recommended procedure for this category is uncertain. The clinician must decide whether to follow the patient for a possible increase in size or to recommend surgical excision. Such decisions are influenced by other suggestive features of potential malignancy discussed earlier.

Inconclusive or Indeterminate There are situations in which, despite the presence of adequate material, the cytological characteristics are not sufficient for diagnosis, as may occur in hyperplastic Hurthle cell nodules, or in which features do not permit distinguishing between adenomatous nodules and follicular neoplasms. The recommended procedure is to repeat the FNA or to recommend surgery if other clinical or sonographic suspicious features are present.

Suspicious for Carcinoma This category refers to cellular atypia, but the number and features of cells are insufficient for a definitive diagnosis of malignancy. It is recommended that surgery be advised in this situation.

Multiple Nodules The management of patients with multiple TNs does not differ from the management of patients with solitary nodules. In the evaluation of multinodular goiters, it is advisable to biopsy nodules showing suspicious features on US as well as the larger nodules. The prevalence of malignancy in nodules from multinodular goiters is comparable to that in solitary nodules: 13% for both categories in 1 study. Cancer was multifocal in 46% of such cases with multiple nodules, and 72% of cancers occurred in the largest (dominant) nodule. It can be concluded that in patients with 1 or more nodules, the likelihood of thyroid cancer per patient is independent of the number of nodules, whereas the likelihood per nodule decreases as the number of nodules increases. For cancer exclusion in a thyroid with multiple nodules larger than 1 cm, up to 4 nodules should be considered for FNA evaluation.

Molecular Markers of Malignancy Immunohistochemical markers for abnormal protein expression (eg, glucose transporters and galectin)

**Table 3. Cytological Categories of FNA Specimens with Suggested Management.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
<th>Suggested Management</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Adenomatous nodule with abundant colloid Cyst, thyroiditis chronic, acute, subacute, or fibrous, or multinodular goiter</td>
<td>Periodic observation including repeated FNA</td>
<td>70% (50%–90%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>Papillary, medullary, or anaplastic carcinomas Lymphoma or rarely metastases</td>
<td>Surgical intervention: almost always total thyroidectomy</td>
<td>5% (1%–10%)</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>Follicular adenoma or follicular carcinoma Oxyphilic cell neoplasm</td>
<td>Surgical intervention: hemithyroidectomy or total thyroidectomy</td>
<td>10% (5%–20%)</td>
</tr>
<tr>
<td>Inconclusive or indeterminate</td>
<td>Cellular adenomatous nodule versus follicular neoplasm Cellular follicular lesion favoring neoplastic nodule Hyperplastic oxyphilic (Hurthle) cell nodule</td>
<td>Consideration of repeat FNA or surgical intervention: hemithyroidectomy or total thyroidectomy</td>
<td>10% (5%–15%)</td>
</tr>
<tr>
<td>Suspicious for carcinoma</td>
<td>Suspected papillary or medullary carcinoma</td>
<td>Consideration of surgical intervention</td>
<td>2% (0%–5%)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Cellular atypia with insufficient cellularity Insufficient material for diagnosis</td>
<td>Repetition of FNA</td>
<td>10% (5%–30%)*</td>
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*Abbreviation: FNA, fine needle aspiration.

*This can be reduced by rebiopsy.

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have been uniformly disappointing in comparison with direct cytology. However, with the identification of V-raf murine sarcoma viral oncogene homolog B1 (Braf) and rearranged during transfection/papillary thyroid carcinoma (Ret-PTC) mutations in up to 70% of papillary thyroid cancers, the era of molecular diagnostics is upon us. Preliminary studies indicate that polymerase chain reaction analysis of FNA samples can contribute to the identification of malignancy. However, to date, the sensitivity of such testing does not match the cytological assessment but may contribute to the identification of high-risk patients. In the near future, molecular markers will likely succeed the cytological approach, but they are not yet part of the routine TN evaluation.

TREATMENT APPROACH

The treatment plan may depend on the patient's age and gender and the characteristics of the nodule (cytology, size, consistency, activity, and number). However, the diagnosis given by the cytologist is the most reliable indication for treatment. The clinical criteria should prevail only when cytological study is inconclusive. However, it is fair to say that there remain significant differences between subspecialists in treatment preferences and that this reflects the lack of evidence-based medicine in this area.

Asymptomatic benign euthyroid TNs need only a watchful follow-up with annual or biannual US and TSH testing. Nevertheless, on some occasions benign TNs do require therapeutic intervention, especially when they grow large and low and when they cause obstructive symptoms.

Any type of malignancy (or when malignancy cannot be ruled out) indicates the need for surgical resection. The extent of surgery depends, in some centers, on the type of tumor. Simple hemithyroidectomy may be recommended as the initial step for a follicular neoplasm or as the definitive treatment for a small, isolated papillary carcinoma if no other risk factors are present. All other thyroid malignancies deserve total thyroidectomy with complementary local node resection. If the histology of the follicular neoplasm confirms the presence of carcinoma, then a total thyroidectomy should be completed. The characteristics of the commonest treatments for TNs are summarized in Table 4.

Surgery

Indications

There are 4 major indications for thyroid surgery in patients with TNs:

1. Suspected malignancy.
2. Large goiters that generate local compressive symptoms.
3. Toxic nodules in young patients.
4. Recurrent cysts after ineffective therapeutic aspirations of the fluid because these lesions may have malignant cells in up to 10% of cases.

Precautions

In addition to the routine potential complications of thyroid surgery, including hypoparathyroidism (temporary or permanent) and damage to the recurrent laryngeal nerve (temporary or permanent), long-term compression of the trachea may lead to atrophy and tracheal collapse after surgery.

Efficacy

Recurrence is common (15%–40%) in inadequately removed multinodular goiters. A second intervention increases the chance of complications. Hence, we recommend a total thyroidectomy as the initial procedure in patients with bilateral nodules. Presurgical thyroxine administration has been suggested to reduce the gland size and consequently the surgical risk, but there is no evidence to support this approach. Also, postsurgical thyroxine is often prescribed with the idea of suppressing any future nodule formation. Although this is logical, the evidence for this maneuver is also absent.

Advantages

In addition to immediate relief of symptoms and concerns, surgery provides a gland for pathological evaluation.

Disadvantages

This is an expensive procedure that usually requires at least overnight hospitalization. The associated morbidity and efficacy are heavily dependent on the surgeon's experience. The main complications are lesions of the recurrent nerve (1%) and in total surgery the problem of permanent hypoparathyroidism (1%). The development of postsurgical hypothyroidism is dependent on the amount and quality of the remaining tissue (only ∼1% with hemithyroidectomies).

Radioiodine $^{131}$I

Indications

The main indications for radioiodine ablation are as follows: (1) hyperfunctioning multinodular goiters

DOI:10.1002/MSJ
Table 4. Characteristics of the Commonest Treatments for a Thyroid Nodule.

<table>
<thead>
<tr>
<th>Main indications</th>
<th>Surgery</th>
<th>Radioiodine</th>
<th>Thyroxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected malignancy</td>
<td>Hyperfunctioning nodule or multinodular goiter (especially in the elderly)</td>
<td>Graves' disease</td>
<td>When no other treatment option is possible in a euthyroid patient</td>
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<tr>
<td>Large goiter</td>
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<td>Toxic nodules</td>
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<td>Recurrent cyst</td>
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<tr>
<td>Graves' disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Surgical contraindications</td>
<td>Pregnancy and lactation</td>
<td>Low plasma TSH level</td>
<td></td>
</tr>
<tr>
<td>Excellent [recurrences are common with incomplete thyroidectomy (15%–40%)]</td>
<td>50% goiter reduction after 1 year</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td></td>
<td></td>
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<tr>
<td>Excellent [recurrences are common with incomplete thyroidectomy (15%–40%)]</td>
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<tr>
<td>Size reduction of 15%–40% but recurrence if treatment is stopped</td>
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<td>Low cost</td>
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<tr>
<td>Possible prevention of new nodule formation</td>
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Advantages

Immediate relief of symptoms
Availability of definitive histologic diagnosis
Repeat treatment feasible
Well-tolerated
Induction of osteopenia and atrial fibrillation
Lifelong treatment
Nodule malignancy must be ruled out before treatment.
Pretreatment with rhTSH may improve the outcome.

Disadvantages

High cost: required hospitalization
Surgery-associated risks: vocal cord paralysis (1%) and hypoparathyroidism (1%)
Hypothyroidism
Recurrences possible
Secondary effects: hypothyroidism (50%–90%), thyroiditis (1%–3%), transient enlargement, and Graves' disease (1%–5%)
Less effective in large goiters

Other considerations

Nodule malignancy must be ruled out before treatment.
Pretreatment with rhTSH may improve the outcome.

Abbreviations: rhTSH, recombinant human thyroid-stimulating hormone; TSH, thyroid-stimulating hormone.

(for which it may be the treatment of choice); (2) hyperfunctioning single nodules; and (3) the need to reduce the size of a normally functioning multinodular goiter that is causing cosmetic or obstructive difficulties for the patient, especially when surgery is contraindicated. Generally, RAI is a preferred therapeutic option for elderly patients.

Precautions

Before RAI administration, any possibility of malignancy should be ruled out. Pregnancy is of course a contraindication, but the fear of developing obstructive problems after the administration of the radiiodine is not justified by experience. Radiation-induced transient thyroiditis, with a tender gland and increased thyroid hormone levels, may develop in the week following treatment of a toxic multinodular gland, but this is more often seen after the treatment of Graves' disease.

Dose

For RAI, 100 to 200 μCi of 131I therapeutic activity per gram of thyroid tissue is often recommended. Generally, to ablate a gland, treatment with 20 to 30 mCi achieves >90% success.

Efficacy

The success of radiiodine treatment depends on many factors other than the 24-hour radiiodine uptake. These include the administered dose and TN consistency because cystic and fibrotic areas will be more resistant to shrinkage. The decrease in nodule size after the procedure is directly related to the dose and inversely related to the initial nodule size. In small (<100 g) multinodular goiters, the typical reduction is about 50%, and the efficacy of the second dose is comparable to that of the first. The shrinkage normally starts in the first weeks, but the maximum result may not be achieved for 1 to 2 years. Around 15% to 30% of patients require a second dose unless maximum ablation is the goal.

Advantages

This is a simple and cheap procedure that does not require hospitalization.

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Disadvantages
If the physician is aiming for euthyroidism, he will be disappointed. The longer the patient is followed, the greater the likelihood of hypothyroidism developing. Using size-related doses causes mild hypothyroidism in 10% to 40% of cases, whereas overt hypothyroidism occurs in up to 50% of patients. Thyroid failure develops mostly in the first 2 years after treatment. Hypothyroidism is particularly frequent in those who have small goiters, anti–thyroid peroxidase antibodies, and/or a family history of thyroid autoimmunity.

Transient thyrotoxicosis, thyroid swelling, neck pain, and tenderness may be seen during the first month after RAI in 10% of cases, but postradiation inflammation and swelling that would require decompressive surgery are not seen. Long-term studies have shown that the associated risk of non–thyroid cancer development after RAI treatment is small. However, around 1% to 5% of patients treated with lower doses of RAI may develop Graves’ disease, which is presumably precipitated by the release of thyroid autoantigens and other immunogenic effects of radioiodine on thyroid-autoreactive lymphocytes. Graves’ disease with nodules is a known clinical entity of 2 common disorders developing together, and RAI may cause subclinical Graves’ disease to worsen. This reaction is seen at 3 to 10 months after 131I administration and is more frequent in anti–thyroid peroxidase–positive subjects.

Utility of Recombinant Human Thyroid-Stimulating Hormone (Thyrogen)
Pretreatment with recombinant human thyroid-stimulating hormone offers the prospect that radioiodine treatment of nontoxic nodular goiters can be simplified and improved, although more information about this strategy is needed. However, this is particularly important in patients with multinodular goiters and low RAI uptakes who would be best treated with RAI. Some studies of nontoxic goiters have shown that pretreatment with 0.03 mg of recombinant human thyroid-stimulating hormone increases the RAI uptake to such an extent that it allows an RAI dose reduction of 60% and improves thyroid size reduction by 35% but with a 5-fold increase in the rate of early hypothyroidism.

Other Options
Thyroxine
The rationale for this strategy is to suppress the TSH stimulatory effect on the TN by providing an excess of thyroxine in the circulation to suppress endogenous TSH levels. This strategy does not work well, and where it has been shown to work, any effect is lost after withdrawal of thyroxine. Suppressing TSH in this way causes atrophy of the normal thyroid, and this may give the incorrect appearance of the nodule becoming smaller. Given the associated risks of high thyroid hormone levels (eg, arrhythmias and bone thinning), routine thyroxine use is not recommended because such side effects overcome the benefits. There are also data suggesting that thyroxine can reduce multinodular goiter size by 15% to 40% in approximately 50% of subjects, but once again this is likely to be mostly due to a reduction in the normal thyroid tissue, and the same side effects are apparent.

Ethanol
The injection, under US control, of ethanol into a TN may be a painful procedure. The size of the nodules may be reduced by 50% in 50% of patients, but usually this needs repeated sessions, sometimes up to 12. The danger of local fibrosis and scarring of the recurrent laryngeal nerve has reduced enthusiasm for this procedure at the present time.

Laser Therapy
Ultrasonographically guided interstitial laser photocoagulation has been used as a nonsurgical alternative in the treatment of benign, solitary, solid (both cold and hot) TNs in patients who cannot (or will not) undergo surgery. The technique has the advantage of not inducing hypothyroidism, but the efficacy is inferior to 131I in normalizing TSH in patients with hot nodules. This procedure warrants further investigation.

The Follow-Up
The follow-up of benign euthyroid TNs depends on the clinical, US, and cytological characteristics described earlier. Usually, TNs require re-evaluation every 6 to 18 months by clinical assessment (history and physical examination), US, and TSH. Nodules that have been cytologically labeled as inadequate, inconclusive, or indeterminate may need more careful monitoring and repeat biopsies.

Substantial growth detected by US (defined as an enlargement of more than 20% or more than 2 mm) does not necessarily indicate malignancy because benign lesions also grow larger, but a repeat FNA should be considered. The same recommendation is valid if new clinical or US features of malignancy appear.

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Thyroid function should also be regularly investigated (usually yearly) in those patients who have been treated with ablative options (surgery or 131I). This is generally evaluated by a serum TSH determination. If hypothyroidism shows up, treatment should be started with thyroxine replacement therapy, which itself also requires annual follow-up. Postoperative US is useful in monitoring the evolution of the remaining gland.

CONCLUSIONS

The adequate initial management of TNs requires a basic clinical and laboratory investigation including a US image and cytological assessment to rule out malignancy. Treatment should be individualized according to both the patient’s and nodule’s characteristics because there are several therapeutic options. Usually, a yearly evaluation is sufficient for long-term follow-up.

DISCLOSURES

Dr. Davies is a consultant of Kronus Corp, Boise, Idaho who distribute thyroid diagnostics.

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