Section 7  Endocrinology

Chapter 63

Guidelines for Management of Thyroid Nodules in Adults: Towards a Consensus

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ABSTRACT

A thyroid nodule could present in different ways: ranging from a solitary, asymptomatic nodule to a large multinodular goiter. This article will suggest guidelines on management of thyroid nodules, based on an already-published national consensus statement co-authored by the present author and will attempt to incorporate recent changes in the diagnostic approach. While approaching a patient with a thyroid nodule, it is important to discern certain clinical features/risk factors suggesting thyroid cancer. Serum thyroid stimulating hormone (TSH) estimation is helpful as an initial test. Fine-needle aspiration biopsy (FNAB) is the best diagnostic test. Ultrasound evaluation is ideal to ascertain risk of malignancy and to improve the precision of the FNAB. In indeterminate cases, thyroid scintigraphy is useful. After the FNAB, surgery is the treatment of choice in malignant and suspicious cases. Surgery is also indicated where there are pressure effects and occasionally for cosmetic reasons. In recent times, total thyroidectomy is preferred for treating multinodular goiters. Treatment with radiodine for reducing goiter size is being researched and may be reserved for smaller goiters, or where surgery is contraindicated. Medical treatment with levothyroxine to suppress the goiter therapy is not a good choice, given the modest benefits and the long-term risks of bone loss and atrial fibrillation. The future would see the use of gene expression classifier tests as an adjunct to conventional FNAB. These newer tests could help foretell whether the thyroid nodule is benign or malignant, thus improving the accuracy of decisions regarding thyroid surgery.

DEFINING THE THYROID NODULE AND ITS EPIDEMIOLOGY IN INDIA

A clinically or radiologically discernable lesion within the thyroid gland is called a thyroid nodule. The term goiter describes the swelling of the thyroid gland. A patient with a thyroid nodule may present with varied manifestations, ranging from a solitary nodule to a large multinodular goiter. In India, thyroid nodules are very common. About 12% of the population has a palpable thyroid nodule. On ultrasound-based assessment, however, the prevalence of thyroid nodules is higher—from about 18.9% in iodine sufficient area like Kerala, to about 80% when a North Indian population with a high prevalence of malnutrition and iodine deficiency was studied. In contrast to thyroid nodules, thyroid cancer is rare in India and the frequency is estimated at 1 per 100,000 for men and 1.8 per 100,000 for women. In the evaluation of the thyroid nodule, the clinical challenge lies in identifying subjects at high risk of developing thyroid cancer. This article will suggest guidelines, based on the already-published Endocrine Society of India’s management guidelines for thyroid journal: the author of this article had co-authored the guideline that has been published.

In addition, recent developments in the management of thyroid nodules (that have been published since the publication of the consensus statement) will be included in this chapter.

DECIDING THE NODULES REQUIRING EVALUATION

All palpable thyroid nodules require investigations. In cases where nodules are not palpable, but are discovered incidentally on scanning, a size-based cut-off has been used to decide upon investigation. A thyroid nodule that is more than 1 cm requires evaluation. However, even in nodules that are below 1 cm in size, evaluation is required if there are any clinical or radiological features (see later) that may heighten the suspicion of thyroid cancer. Common causes of thyroid nodules are listed in Table 1.

CLUES FROM THE CLINICAL ASSESSMENT

Clinical information is very important everywhere, but in a country like India, where state of the art clinical facilities do not abound in every nook and corner, clinical assessment is quintessential. Certain features are considered risk factors for thyroid cancer: family history of thyroid cancer, rapidly enlarging nodule, firm/hard nodule, fixity to surrounding structures, hoarseness of voice, regional lymph node enlargement or the presence of another lesion (for e.g. a lung mass on respiratory examination) that suggests a distant metastases. While the abovementioned features are classical features, it must be remembered that many patients do not come with these typical features and the presence of the following factors in addition to the thyroid nodule suggests the need for further investigations: a history of radiation, male gender, extremes of age (< 20 or > 70 years), history of neck irradiation, clinically, the nodule being larger than 4 cm in size or the presence of any pressure symptoms.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Some important causes of thyroid nodules</th>
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<tbody>
<tr>
<td>Nodules of benign etiology:</td>
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<tr>
<td>Follicular adenoma</td>
<td>Nontoxic/toxic multinodular goiter</td>
</tr>
<tr>
<td>Colloid nodule</td>
<td>Thyroiditis</td>
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<tr>
<td>Hyperplastic nodule</td>
<td>Lymphoma</td>
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<td>Nodules of malignant etiology:</td>
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<tr>
<td>Follicular thyroid cancer</td>
<td>Anaplastic cancer</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>Other cancer/metastasis</td>
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</table>
Thyroid function tests are mandatory. A TSH value that is low indicates hyperthyroidism and a TSH that is high indicates hypothyroidism. The ultrasound of the neck (ultrasonography (USG)) is useful, for it can assess nodule size and number. Combining the USG with a Doppler improves the estimation of malignant potential: risk of malignancy is lower when a nodule has an exclusively perinodular vascular pattern than when there is a purely central vascular pattern. The following USG patterns suggest malignancy: infiltration into regional structures, ill-defined borders, irregular shape, hypoechogenicity, heterogeneous internal echoes, microcalcifications, absence of a halo, solidity, an anteroposterior to transverse diameter ratio (A/T) greater than 1, and suspicious regional lymph nodes. The investigations used to diagnose a thyroid nodule must be carried out in a systematic manner. Fine needle aspiration biopsy is the most ideal test for diagnosing the etiology of the thyroid nodule. Any nodule that is larger than 1 cm must be subjected to FNAB. Smaller, non-palpable nodules in an ultrasound require evaluation in the presence of any high-risk characteristics. Ultrasonography-guided FNAB can further lower the occurrence of nondiagnostic smears. Degenerating and cystic nodules are sometimes challenging. In this setting, the accuracy is improved by using ultrasound-guided aspirations from solid zones. Overall, a USG-guided FNAB with an immediate confirmation of adequate cellularity of the smear by a trained cytopathologist is the investigation with the highest sensitivity and specificity. In suspicious nodules, taking multiple aspirates will help to improve the test. In multinodular goiter, the following criteria may be used to decide on the better nodule for FNAB in the order listed: nodules more than 1 cm in largest diameter with microcalcifications, nodules larger than 1.5 cm that are predominantly solid or having coarse calcifications, nodules larger than 2 cm which are mixed solid cystic or have undergone “substantial” growth since last ultrasound or the largest nodule. It is important to note that the presence of multiple nodules does not decrease the risk of thyroid cancer. Nuclear scanning may be considered in selected cases (especially when the TSH is low); these scans use isotopes of iodine or technetium. These are handled differently by the follicular cells. Normal follicular cells take up both, but only radioidine is organified and stored. Most benign and malignant neoplasms concentrate isotopes less avidly leading to a “cold” area on scanning. The rate of malignancy is about 10–15% in cold nodules, whereas malignancy is less likely in hot nodules. A hot nodule suggests hyperthyroidism: such nodules are usually not malignant. In large nodules, it is useful to assess if airways have been obstructed: plain radiography of the thoracic inlet and respiratory flow volume loops can detect patients who are having functional tracheal compression who may need surgery.

**PALPATION-GUIDED FNAB VERSUS ULTRASOUND-GUIDED FNAB**

Wherever available, USG-guided FNAB is ideal and preferable to palpation-guided FNAB. However, in a country like India, where expensive tests are often difficult to order and a practical approach is important. Thus, in selected cases, where cost is a concern, palpation-guided FNAB may be considered. It is important, however that this be reserved for solitary, large nodules. In some situations, palpation-guided FNAB should never be considered and USG-guided FNAB is mandatory: non-palpable nodules, nodules with more than 25% cystic change, previously FNAB-inconclusive nodules as well as suspicious nodules. The paradox here is that to detect the nodules with 25% cystic change as well as to detect the suspicious nodules and ultrasound examination is mandatory. Hence, with the ever increasing importance of USG of the thyroid, USG scanning is becoming mandatory in all thyroid nodules and therefore, USG-guided FNAB is the diagnostic procedure of choice in the majority of cases.

**A SIMPLIFIED ALGORITHM**

A simplified algorithm is given in **Flow chart 1**. The algorithm is adapted from the position statement of the Endocrine Society of India management guidelines for thyroid nodules. However, algorithms are only a generalization and an individualized assessment is important.

**TREATMENT OF THYROID NODULES**

The management depends on the FNAB report. In FNAB reports suggesting **malignancy** or **suspicious** cytology, surgery is the ideal option. In **benign** cases, follow-up may be an option, although surgery remains the option for permanent cure. Where there are pressure effects, surgery is the treatment of choice. In **nondiagnostic** FNABs, every effort must be made to follow-up the patient carefully, with periodic repeated attempts at FNAB. A dilemma emerges when the FNAB reports a follicular lesion or a Hurthle cell nodule. In these cases, the differentiation between benign adenoma and cancer requires histological demonstration of vascular/capsular invasion. Surgery is ideal in these cases. Also, a fast rate of enlargement and the onset of pressure symptoms (voice change, breathing difficulty, etc.) will signal the need for surgery. In malignant/suspicious cases, total thyroidectomy is the treatment of choice. A rare exception to the rule of total thyroidectomy is a case of a papillary thyroid microcarcinoma (< 1 cm) in the absence of local invasion. In this situation, the American Thyroid Association suggests lobectomy. The choice of surgery (total or hemi- or subtotal thyroidectomy) in subjects with a benign cytology is a little controversial. In recent

**Flow chart 1:** Management of thyroid nodule: a simplified algorithm. At any level, an intermediate result can justify the use of nuclear scintigraphy. Please note that even subjects with a low TSH and a thyroid nodule require USG-guided FNAB, except when clinical features, nuclear scintigraphy and antibody test reveal a classic case of thyroiditis, Graves’ disease or a solitary toxic nodule.
years, the specialists are increasingly showing their preference for total thyroidectomy, even for bilateral benign multinodular goiters.⁸ The reasons could be because of the heightened awareness of the possibilities of hyperplasia of the residual tissues or a histological surprise (an unexpected finding of malignancy in what is otherwise a clinically classical multinodular goiter) may anyway make completion thyroidectomy mandatory. The risks of thyroidectomy (recurrent laryngeal nerve injury and hypocalcemia due to parathyroid damage) could be higher when a surgery is performed on the thyroid for the second time.

**NONSURGICAL TREATMENT OF THYROID NODULE**

Using thyroxin suppression therapy to reduce the size of thyroid nodules is not considered as an optimal strategy.⁹ The disadvantages of suppressive levothyroxine therapy are mild efficacy, need for long-term therapy, post-therapy regrowth, risk of tachycardia and osteoporosis. An emerging area of treatment is with radioiodine (I-131) therapy. Treatment with radioiodine may be a consideration in mildly enlarged, benign thyroid swellings, but benefits are limited by the very slow action and the need for contraception in female subjects. Ethanol injection into nodules (especially the symptomatic cystic nodules) may be useful. This can reduce the goiter size by 45% at the end of 6 months, but has severe adverse effects: seepage of ethanol, hemorrhage into nodule, pain and even vocal cord paralysis. Laser therapy of thyroid nodules is experimental. It is possible that laser therapy is useful in debulking of benign thyroid nodules with local pressure symptoms especially where surgery is contraindicated or has been refused. The long-term advantages of laser treatment of thyroid nodules are currently unknown.

**THYROID NODULE MANAGEMENT IN SPECIAL SITUATIONS**

Thyroid swellings can enlarge in pregnancy. A TSH is the best initial test. No further evaluation is indicated for the nodule if the TSH is suppressed, except to rule out hyperthyroidism. Nodules detected during the third trimester can be evaluated after completion of pregnancy as such delay is not expected to significantly affect the prognosis even if the nodule turns out to be malignant. If the nodule is detected in the first or second trimester, treatment is more complex. If the TSH is normal or high in this setting, a FNAB is indicated. If FNAB suggests malignancy, the patient should be on levothyroxine suppressive therapy with levothyroxine and surgery considered in the second trimester. If the FNAB report is benign, no further evaluation is needed during pregnancy except levothyroxine to normalize the TSH. Evaluation after delivery may proceed in as indicated in the general guidelines in nonpregnant adults.¹⁰

A second special situation is the management of cystic thyroid swellings.¹¹ Most cystic lesions are degenerating benign adenomas. An ultrasound can help characterize the cystic thyroid lesion. Solid-cystic thyroid nodules have a higher risk of malignancy than the purely cystic nodules. Ultrasonography can differentiate between a solid and cystic lesion. However, 80% of thyroid nodules are solid/solid-cystic. Hence, if the ultrasound report is the sole criteria to decide about surgery then 80% of patients may eventually be candidates for surgery. A better option is to perform an FNAB from the solid portion of the solid-cystic lesion using USG guidance and then decide on therapy in all cystic thyroid lesions. In cases of persistent, uncharacterized cystic lesions, surgery is ideal.

A final issue is the management of thyroid incidentalomas which are incidentally detected thyroid nodules on ultrasound, CT scans or even positron emission tomography (PET) scans. It is possible that PET scan detected incidental thyroid nodules may have a higher possibility of being malignant further research is needed to clarify these nodules and their prognosis. A general management approach is to observe those nodules that are less than or equal to 1 cm in size and perform an FNAB under ultrasound guidance for nodules greater than 1 cm. If high-risk features exist, then even nodules below 1 cm will require ultrasound examination. The prevalence of malignancy in subjects with a nonpalpable nodule is the same as that in a palpable nodule: this means that the patient should be closely monitored with frequent follow-ups and ultrasound studies to ascertain any change in size or onset of atypical ultrasound features.⁶

**EXPECTATIONS FROM FUTURE MODALITIES**

A drawback in the evaluation of thyroid nodules is the occurrence of indeterminate cytological diagnoses (as high as nearly 15%) on FNAB. While radionuclide scanning has been an important tool in distinguishing benign from malignant cases in the indeterminate setting, it has not established pre-eminence as a gold standard. Hence, immunocytological studies (particularly with galectin-3 immunostaining) and molecular cytogenetic studies (BRAF, RAS, RET/PTC and PAX8/PPARγ mutations) have been used to improve the accuracy of the traditional FNAB. These two modalities have been important in taking the FNAB-innovation research to a higher level. Another recent advance has been treatment with recombinant TSH (r-TSH): this can augment the effect of radioiodine for reducing the size of benign goiters. Recombinant TSH can increase the uptake of iodine by thyroid cells and can thus augment the effect of I-131 on nodule size.¹²,¹³ This could be an attractive option in reducing large benign goiters, where surgery has been refused or is contraindicated. Whether r-TSH is now available in India, treatment is expensive, experimental and therefore ridden with controversy.

However, the most exciting advancement in the management of thyroid nodules has been a new presurgery prediction tool. In essence, it is still an innovation on the traditional FNAB. However, the test uses a combination of 167 genes to decide on preoperative assessment of malignant potential. The test has been recently validated in a multicenter study with 577 specimens with indeterminate cytology setting, it has not established pre-eminence as a gold standard. Hence, immunocytological studies (particularly with galectin-3 immunostaining) and molecular cytogenetic studies (BRAF, RAS, RET/PTC and PAX8/PPARγ mutations) have been used to improve the accuracy of the traditional FNAB. These two modalities have been important in taking the FNAB-innovation research to a higher level. Another recent advance has been treatment with recombinant TSH (r-TSH): this can augment the effect of radioiodine for reducing the size of benign goiters. Recombinant TSH can increase the uptake of iodine by thyroid cells and can thus augment the effect of I-131 on nodule size.¹²,¹³ This could be an attractive option in reducing large benign goiters, where surgery has been refused or is contraindicated. Whether r-TSH is now available in India, treatment is expensive, experimental and therefore ridden with controversy.

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REFERENCES


