Chapter

# Thyroid Nodule: Approach and Management

*Madhukar Mittal, Vanishri Ganakumar, Ravindra Shukla and Mahendra Kumar Garg*

## Abstract

A thyroid nodule is a discrete radiologically distinct lesion in the gland parenchyma. These are a common finding in the general population, majority being diagnosed incidentally during neck imaging. The major clinical relevance lies in the fact that 4–6.5% of nodules can be malignant. A thorough clinical evaluation and examination should be followed by serum TSH assessment and ultrasonography for assessment of size, number, imaging characteristics suggestive of malignancy, cervical lymphadenopathy. FNA should be done based on clinical and sonographic characteristics. Further choice of management modality and extent of surgery should be based on cytopathological findings supplemented by molecular testing if available.

**Keywords:** thyroid nodule, toxic adenoma, multinodular goitre, thyroiditis

## 1. Introduction

A thyroid nodule is defined as a discrete radiologically distinct lesion from the surrounding thyroid parenchyma. Nodules which are palpable but do not correspond to distinct abnormalities on ultrasound do not fall under this category [1]. Clinically they can be identified by the doctor on examination or even noticed by the patient themselves. With the increasingly popular use of neck imaging modalities, thyroid nodules are being commonly identified during these imaging studies.

The clinical importance lies in excluding malignancy in a thyroid nodule, assessing functional status, associated with pain at appearance and compressive symptoms (if large) and accordingly decide the line of management. The key guidelines included to cover this area include

1. The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer.

2. AACE/ACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules-2016 update [2].

3. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee [3].

4. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: The EU-TIRADS [4].

This chapter thus provides a comprehensive coverage of the topic with an optimal approach in management of a thyroid nodule.

## 2. Epidemiology

Thyroid nodules are a common finding in general population. This is likely due to the increased use of diagnostic imaging for purposes unrelated to the thyroid. The prevalence of thyroid nodules in a population depends on the screening method used and the presence of risk factors for nodule development. The prevalence of thyroid nodules by palpation was found to be 4.2% in a population-based study in Framingham. The prevalence in females and males was 6.4 and 1.5%, respectively [5]. Clinically nonpalpable nodules are frequently identified on ultrasonography and are termed "incidentalomas." The prevalence of thyroid nodules as detected by high resolution ultrasound can be as high as 67% [6]. The prevalence in this Californian study also had an asymmetrical distribution with 72 and 41% prevalence in females and males respectively. 22% patients had solitary nodules, whereas 45% had multiple nodules. In another Italian study by Bartollota et al., the prevalence of thyroid nodules by ultrasonography was 33.1%. Thus it becomes a difficult dilemma on what to do with incidentally detected thyroid nodules which are not malignant and not well-characterised.

Also the number of detected nodules increases with age, with the highest prevalence in the seventh decade. Autopsy studies provide the true prevalence of the incidence in a population. An autopsy study in Mayo clinic revealed a prevalence of around 50% even in patients with no history of thyroid disease [7, 8]. This makes it even more complicated that many individuals would complete their lifespan without any intervention for their thyroid nodules.

## 3. Risk factors

The prevalence of thyroid nodules is 4 times more common in females than in males. Gender disparity is postulated to occur secondary to influence of oestrogen and progesterone, as demonstrated by increased risk associated with pregnancy and multiparity [9]. The prevalence of thyroid nodules increases with age. Nodules occur more commonly in areas of iodine deficiency. Cigarette smoking can also predispose to development of nodular goitre. This can occur secondary to inhibition of iodine uptake and organification by thiocyanate, which is derived from cyanide in cigarette smoke, hence mimicking iodine deficiency [10]. Obesity has also been demonstrated to be associated with increased risk of goitre and thyroid nodules [11, 12]. Serum IGF-1, being a potent mitogenic factor, was postulated to be associated with development of thyroid nodules. A positive association was observed between serum IGF-1 levels and prevalence of thyroid nodules in males in a study by Volzke et al. In a study by Ying Jian Liu et al., serum IGF-1 levels were not found to be significantly different in patients with hot nodules, cystic cold and solid cold nodules. However, in subgroup analysis, patients with thyroid adenoma on FNA were found to be having significantly higher serum IGF1 levels compared to the control group comprising of healthy adults. However no such association was demonstrated in a study by Hsiao et al. [13–15]. On the other hand, alcohol intake has been associated with decreased prevalence of goitre and thyroid nodules [16].

Autoimmune thyroid diseases are commonly associated with thyroid nodules. Graves disease is associated with nodules in 10–31% of patients. In a Brazilian study, the prevalence of nodules in Graves disease was 27.8%; 19.5% of the nodules harboured thyroid carcinomas, yielding an overall malignancy prevalence of 5% in patients with Graves disease. Younger age and increased thyroid volumes were associated with increased risk for papillary thyroid carcinoma (PTC). This was in contrast to other studies where older age was a risk factor for malignancy [17, 18]. Small thyroid nodules are also commonly associated with Hashimotos thyroiditis. These should be differentiated form pseudonodules resulting from inflammatory infiltrate. Despite the concerns, the US Preventive Services Task Force (USPSTF), which reviews the effectiveness of screening programs in asymptomatic individuals, recommended against screening for thyroid cancer in adults without signs or symptoms of the disease [19].

## 4. Aetiology

Thyroid nodular disease comprises of a wide range of disorders. Colloid nodules, cysts and thyroiditis comprise of 80% of cases, whereas benign follicular neoplasms and thyroid carcinomas account for 10–15% and 5% cases respectively [20]. These causes have been summarised in **Table 1**.

| Benign causes | Malignant causes |
|---|---|
| Hashimotos thyroiditis | Papillary thyroid carcinoma (PTC) |
| Colloid adenomas | Follicular thyroid carcinoma (FTC) |
| Cysts | Medullary thyroid carcinoma (MTC) |
| Follicular adenomas | Anaplastic thyroid carcinoma (ATC) |
| Hurthle cell adenomas | Primary thyroid lymphoma |
| | Metastatic carcinomas (breast, renal, lung, head and neck) |

**Table 1.**
*Aetiology of thyroid nodules.*

## 5. Clinical evaluation

Thyroid nodules can present as anterior neck swelling. Most nodules grow very slowly over years. Patients may also present with history of rapid increase in size, which can be suggestive of a malignancy, or a haemorrhage into a nodule, especially if associated with pain. Significant sized nodules can result in compressive symptoms based on the anatomical structure being compromised. Larger nodules can result in compression of underlying structures leading to symptoms like dyspnoea, dysphagia, and hoarseness of voice with compression of trachea, oesophagus and recurrent laryngeal nerves respectively. Patient can also present with thyroid dysfunction. Younger patients with adenoma and thyrotoxicosis (Toxic adenoma) tend to present with the classical symptoms of thyrotoxicosis like nervousness, weight loss despite increased appetite, tremors, palpitations, heat intolerance and sweating. On the other hand, thyrotoxicosis in elderly can present with non-specific symptoms like anorexia, atrial fibrillation, congestive heart failure, and is difficult to diagnose due to lack of classical symptoms. A hypothyroid presentation with fatigue, constipation, cold intolerance is more indicative of a diagnosis of autoimmune thyroiditis in patients with nodular goitre.

| History | Findings |
|---|---|
| Age < 20 years or > 70 years | Nodules >4 cm in size |
| Male sex | Hard consistency |
| Increasing size/rapid growth | Fixed nodule |
| Compressive symptoms: dyspnoea, dysphagia, hoarseness of voice | Vocal cord palsy |
| Childhood H/O exposure to radiation | Regional lymphadenopathy |
| Family H/O thyroid malignancies, MEN2, intestinal polyposis syndromes | Distant metastases |

**Table 2.**
*Risk factors for malignancy.*

Findings suggestive of hyperthyroidism or hypothyroidism should be actively elicited during examination. Size of the gland and qualitative and quantitative description of palpable nodules and lymph nodes should be noted, including size, tenderness, consistency and fixity to surrounding anatomical structures. Smaller thyroid nodules <1 cm, and posteriorly or substernally located nodules can be difficult to palpate, and would be better characterised by imaging techniques.

Increasingly nodules are being detected during neck imaging for other indications. The clinical importance of diagnosis of thyroid nodules lies in excluding malignancy in these patients. 4–6.5% of thyroid nodules can harbour malignancy [1]. History of rapid growth of the nodule, hoarseness of voice due to paralysis of vocal cords suggests a malignant aetiology. Examination features in such cases could include a hard consistency of the nodule, fixation to surrounding structures, presence of regional lymphadenopathy or distant metastases. The risk of a nodule being malignant increases with extremes of age and with male sex. The frequency of malignancy in patients with solitary nodules is not different from nodules seen in multinodular thyroid disease [21].

Other risk factors which impart increased risk of malignancy should be enquired in all patients. History of prior exposure to radiation for various indications like haematopoietic malignancies and stem cell transplantation, head and neck, mediastinal and CNS tumours should be sought, as this increases the likelihood of malignancy in thyroid nodules. Familial forms of thyroid cancers should be considered in differential diagnosis in the presence of supportive history. Most common form of familial thyroid cancers is seen in medullary thyroid carcinomas (MTC). Familial MTC can occur either as an isolated problem inherited in an autosomal dominant fashion, or as a component of MEN 2A (MTC, primary hyperparathyroidism, pheochromocytoma) MEN 2B (MTC, pheochromocytoma, ganglioneuromas, Marfanoid habitus, thickened corneal nerves). Familial papillary thyroid carcinoma (PTC) can occur as an autosomally dominantly inherited isolated form, or can be a component of Pendred syndrome or intestinal polyposis syndromes like Familial adenomatous polyposis (FAP), Gardner syndrome and Peutz Jeghers syndrome. Follicular thyroid carcinoma (FTC) can be associated with Cowden disease and Bannayan Riley Ruvalcaba syndrome. Carney complex type I can be associated with either PTC or FTC, whereas Werner's syndrome can be associated with PTC, FTC or anaplastic thyroid carcinoma (ATC) [22]. Factors suggestive of an increased likelihood of malignancy have been summarised in **Table 2**.

## 6. Laboratory evaluation

### 6.1 Serum TSH

The initial evaluation in all patients presenting with a thyroid nodule should include a measurement of serum TSH. If TSH levels are low, possibility of

subclinical or overt hyperthyroidism should be considered. Approximately 10% of solitary nodules can be associated with a subnormal TSH. Multinodular goitres, on the other hand, are frequently associated with suppressed TSH due to development of autonomy in the nodules. Serum free T4 levels and T3 levels should be obtained for documentation of hyperthyroidism; the latter may especially be obtained in areas with iodine deficiency due to preferential secretion of T3 over T4 in these circumstances. Patients with a thyroid nodule and subnormal TSH can be taken for a Nuclear Thyroid Scan to document the functional status of the nodule.

### 6.2 Serum thyroid antibodies

In patients with elevated TSH, anti-thyroid peroxidase (anti-TPO) antibodies may be measured which point to a diagnosis of Hashimotos thyroiditis. However, positive anti-TPO does not obviate the need for a cytopathological evaluation, as a coexisting malignancy needs to be ruled out. A raised or even a normal TSH is associated with an increased risk of malignancy, as well as a more advanced stage of differentiated thyroid cancer [23, 24].

### 6.3 Serum thyroglobulin

Thyroglobulin (Tg) is a storage form of thyroid hormones, synthesised by thyroid follicular cells. Serum Tg levels are elevated in many benign and malignant thyroid disorders. An elevated level of serum Tg cannot differentiate malignancy in a thyroid nodule with certainty. Measurement of serum thyroglobulin has a role in postoperative monitoring for residual, recurrent or metastatic disease in patients with differentiated thyroid cancers.

### 6.4 Serum calcitonin

Calcitonin is produced by the parafollicular C cells of the thyroid gland and is a marker for medullary thyroid cancer (MTC). Basal and pentagastrin stimulated serum calcitonin has a role in early diagnosis as well as post-operative monitoring of patients with MTC. Serum calcitonin is measured in patients with family history of MTC or MEN-2 syndrome. Unstimulated serum calcitonin levels >50–100 pg/ml are commonly associated with MTC. There are no recommendations for the routine use of calcitonin in evaluation of thyroid nodules in current recommendations.

## 7. Imaging

### 7.1 Radionuclide scan

Hyper-functioning thyroid nodules comprise up to 10% of thyroid nodules. Currently ATA recommends performing a thyroid radionuclide scan in patients with thyroid nodule associated with subnormal TSH. Two radionuclides are primarily used for functional evaluation of thyroid nodules: I123 and Tc 99 m pertechnetate. Both the radioisotopes are taken up by thyroid follicular cells, but only radioiodine is organified and stored within the gland. A thyroid nodule can be classified as "hot/hyperfunctioning", "warm/isofunctioning" and "cold/hypo-functioning" on scintigraphy. A functioning nodule is nearly always benign. 5% of nodules that appear hot or warm on pertechnetate scanning can appear cold on radioiodine scanning, up to 30% of which can be malignant [25].

On the contrary, the risk of malignancy in non-functioning nodules is 4–6.5% [26–29]. Since malignancy is rarely encountered in hyperfunctioning nodules,

further cytological evaluation is not necessary if a corresponding hot nodule is identified on scintigraphy.

### 7.2 Ultrasonography

Ultrasonography has become an indispensable tool for the evaluation of thyroid nodules. Ultrasound is easily available, non-invasive and invaluable for dileniation and prognostication in these patients. Ultrasound in the hands of an experienced sonologist enables accurate identification of size, number of nodules, composition, echogenicity, margins, presence and type of calcifications, shape if taller than wide, vascularity and status of cervical lymph nodes. The pattern of sonographic characteristics of a nodule confers a risk for malignancy. Categories of high suspicion nodules are then subjected to invasive modalities like Fine Needle Aspiration (FNA) and cytological evaluation is done. Features with the highest specificities (median > 90%) are microcalcifications, irregular margins and tall shape, even though the sensitivities are significantly low for any single feature.

Ultrasound is also invaluable in assessing the risk of malignancy in lymph nodes. Location of the lymph nodes adds to the diagnosis. Malignant nodes are more likely to occur in levels III, IV and VI than in level II. PTC tumours arising in upper pole of the thyroid may be an exception as they have a propensity to demonstrate skip metastases to levels III and II. Size of >1 cm, ratio of long axis to short axis (also called as Solbiati index of <2), punctate calcification, presence of hyperechogenicity/mixed echogenicity/cystic changes, loss of hilum and peripheral hypervascularity are some of the features predictive of malignancy. While peripheral vascularity has the highest sensitivity of 86%, punctate calcifications are 100% specific for malignant involvement [30, 31]. However, no single sonographic feature is adequately sensitive for determining malignant involvement. Sonographically suspicious lymph nodes ≥8–10 mm in the smallest diameter should therefore undergo FNA to look for evidence of malignant involvement.

Ultrasound Elastography is a novel modality performed with an ultrasound machine using an elastography computational module. It provides a measure of tissue stiffness, and is being used for malignancy risk assessment. In a study by Azizi et al., thyroid nodule stiffness by elastography was an independent predictor of thyroid carcinoma, with a PPV of 36%, comparable to that of microcalcifications. On the contrary, in another study by Moon et al., elastography alone or in combination with grey scale ultrasound showed an inferior performance compared to grey scale ultrasonographic assessment for differentiation of benign and malignant thyroid nodules [32]. Guidelines currently do not recommend universal use or widespread adoption of ultrasound elastography for malignancy risk assessment.

### 7.3 CT and MRI neck

Since ultrasound is operator dependent and cannot adequately image deep anatomic structures and those acoustically shadowed by bone or air, preoperative cross sectional imaging like CT/MRI can be used as an adjunct in patients with clinical suspicion of advanced disease, like patients with an invasive primary tumour, or clinically apparent multiple or bulky nodal involvement. These modalities permit imaging beyond the routine cervical regions imaged by the ultrasound, like infraclavicular, retropharyngeal, parapharyngeal regions and the mediastinum. These also aid in preoperative planning to accurately delineate the inferior border, extent of laryngeal tracheal, oesophageal or vascular involvement.

Combined ultrasound and CT may have a higher sensitivity for macroscopic nodal metastasis detection preoperatively, compared to ultrasound alone [33, 34].

Contrast enhanced CT helps in the accurate delineation of the primary tumour and the metastatic disease with the surrounding areas. There exists a small risk of precipitating hyperthyroidism due to iodine content in the contrast agents. Iodine from the IV contrast agents is generally cleared within 4–8 weeks of the scan, as assessed by the urinary iodine levels returning to baseline. Hence a waiting period of atleast a month is advisable to allow urinary iodine levels to return to normal before moving forward to the use of diagnostic or therapeutic radioiodine post-operatively. There is no evidence to suggest this could translate into adverse outcome for thyroid cancer patients currently [31, 35]. MRI is prone to respiration artefacts and can be more difficult to interpret by surgeons in the operating room.

### 7.4 FDG PET

Functional imaging with 18 F – FDG PET is currently not recommended routinely prior to initial surgery. However, it has been widely accepted as a modality for detecting recurrence of differentiated thyroid cancer, particularly in non-iodine avid disease. PET avidity has also been shown to be a strong predictor of poor outcome in metastatic thyroid cancer [31].

### 7.5 Guidelines for evaluation, reporting and management of thyroid nodules

Sonographic Scoring systems are used to stratify nodules according to risk of malignancy to allow centres for uniform reporting and reduce interobserver variability.

The **American Thyroid Association (ATA)** risk stratifies nodules into high suspicion, intermediate suspicion, low suspicion, very low suspicion and benign categories based on imaging characteristics. The sonographic features have been shown in **Figure 1** and the FNA cut-offs have been summarised in **Table 3**.

Similar to Breast reporting, the **American College of Radiology** has developed a reporting system for thyroid nodules known as **Thyroid Imaging Reporting and Data System (TIRADS)** for risk stratification based on points assigned for

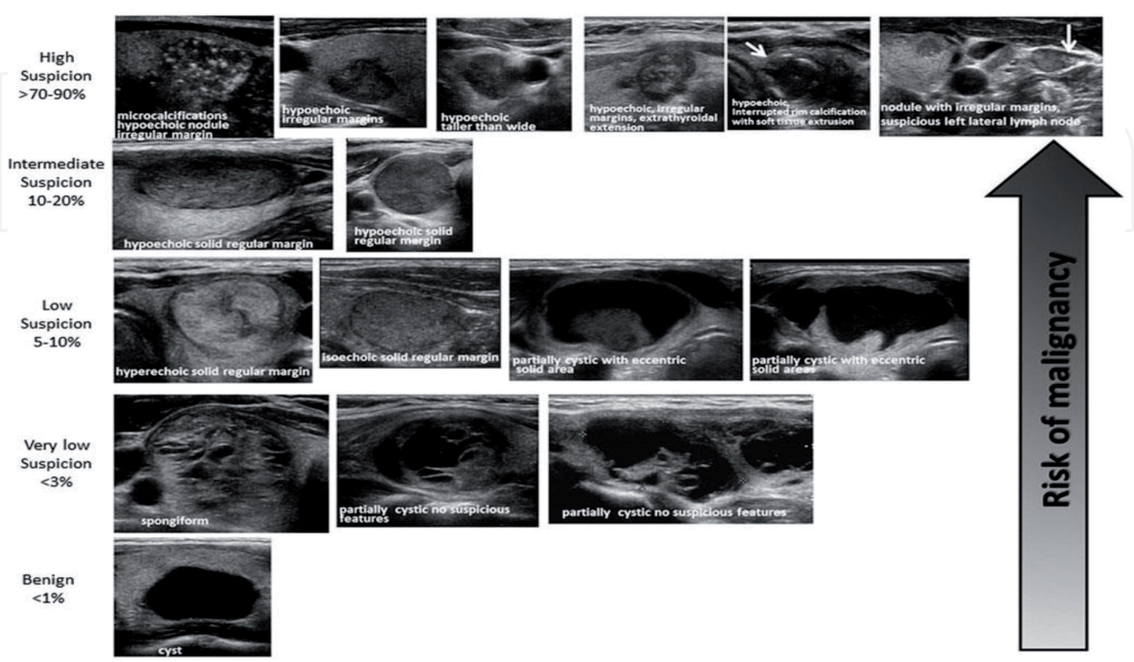


**Figure 1.**
*Sonographic characteristics of thyroid nodules (Adapted from ATA guidelines for adult patients with thyroid nodules and differentiated thyroid cancer [1]).*

| Sonographic pattern | Ultrasound features | Estimated risk of malignancy | FNA size cutoff (largest dimension) |
|---|---|---|---|
| High suspicion | Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following<br>• Irregular margins (infiltrative, microlobulated)<br>• Microcalcifications<br>• Taller than wider shape<br>• Rim calcifications with small extrusive soft tissue component<br>• Evidence of extrathyroidal extension (ETE) | >70–90% | ≥1 cm |
| Intermediate suspicion | Hypoechoic solid nodule with smooth margins, without microcalcifications, ETE, or taller than wider shape | 10–20% | ≥1 cm |
| Low suspicion | Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE or taller than wider shape | 5–10% | ≥1.5 cm |
| Very low suspicion | Spongiform or partially cystic nodules without any of the sonographic features described as low, intermediate or high suspicion patterns | <3 | ≥2 cm/ Observe |

**Table 3.**
*Sonographic characteristics and FNA cutoffs of thyroid nodules Adapted from ATA guidelines for adult patients with thyroid nodules and differentiated thyroid cancer [1].*

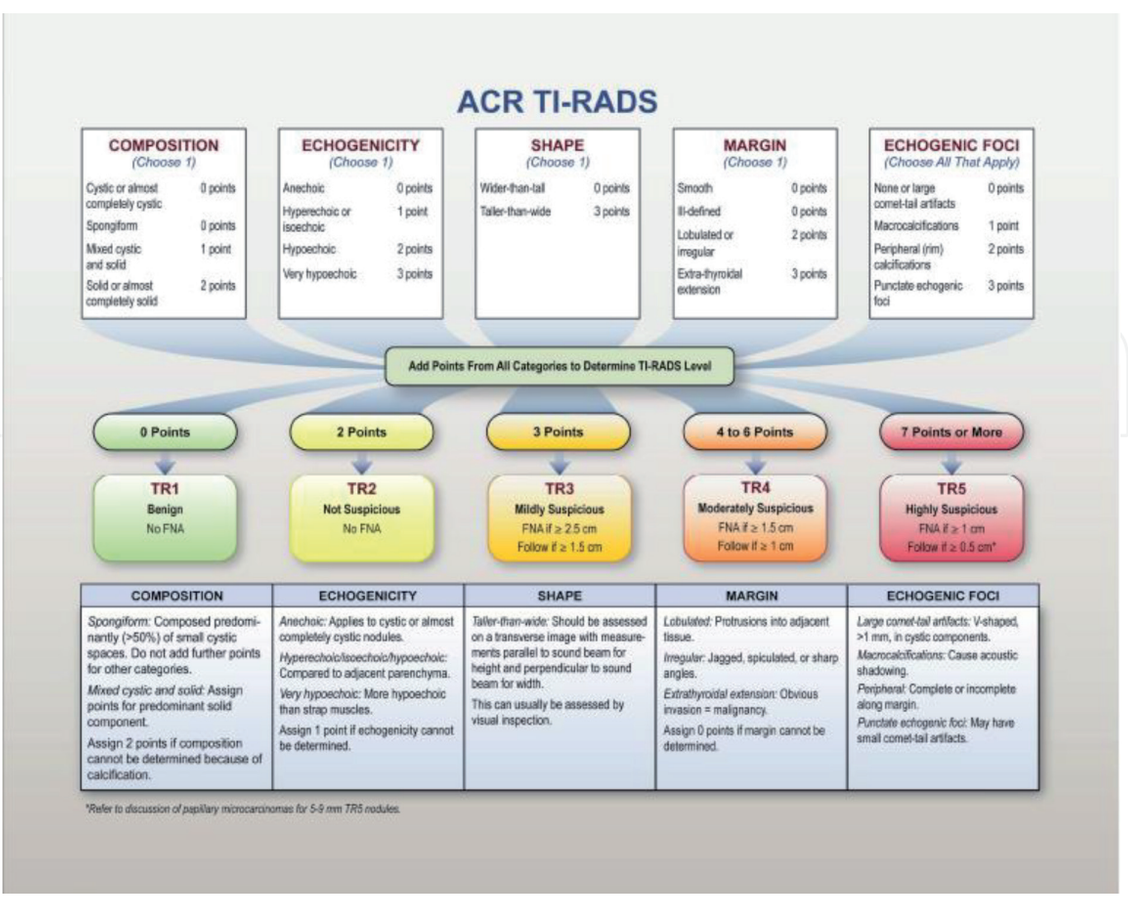


**Figure 2.**
*The ACR-TIRADS scoring system of reporting for thyroid nodules (reproduced from www.acr.org).*

composition, echogenicity, shape, margin and echogenic foci in the nodule. The total number of points is then used to classify a nodule into benign (TR1), not suspicious (TR2), mildly suspicious (TR3), moderately suspicious (TR4), and highly suspicious (TR5) categories. This system was proposed in a study by Horvath et al., and the probability of malignancy was 0, 3.4%, 14% and 87% in categories 2, 3, 4 and 5 respectively [36]. FNA is not indicated in TR1 and TR2 categories, whereas FNAC is advised if nodule size is ≥2.5, ≥1.5 and ≥ 1 cm, respectively, in TR3, TR4 and TR5 categories, respectively. The details of the scoring system are shown in **Figure 2**.

Patients with multiple thyroid nodules ≥1 cm should be evaluated similarly as delineated above for patients with solitary nodule. Each nodule in a multinodular gland carries an independent risk of malignancy, and FNA should be done in sequentially based on imaging characteristics. In case of multiple sonologically similar low or very low risk pattern nodules, aspiration can be done in the largest nodule ≥2 cm, or surveillance can be continued without FNA.

## 8. Fine needle aspiration (FNA)

FNA is the single most valuable, cost effective and accurate method in the evaluation of a nodular goitre. It has demonstrated a sensitivity and specificity of 65–98 and 72–100%, respectively [22]. The use of FNA results in fewer surgeries, reduced cost of care, while improving the malignancy yield at thyroidectomy [37]. Selection of which nodule to subject to FNA is crucial for optimum yield of the procedure. This is based on the sonographic criteria and the size cut-offs depending on which guideline one follows.

FNA is done as an outpatient procedure under local anaesthesia or no anaesthesia. 23–27 guage needles are used to obtain samples for cytopathology. For nodules with a high likelihood of non-diagnostic cytology (>25–50% cystic component) or sampling error (difficult to palpate or posteriorly located), ultrasound guided FNA is preferred [29].

To address variability in reporting thyroid cytopathology, **Bethesda System for reporting thyroid cytopathology** was introduced in 2007. Cytologic adequacy for reporting was defined as presence of at least six groups of well visualised follicular cells, each group containing at least 10 well preserved epithelial cells, preferably on a single slide. The Bethesda system recognises six diagnostic categories and provides an estimation of cancer risk within each category, which has been summarised in **Table 4**.

| Diagnostic category | Estimated risk of malignancy by Bethesda system, % | Actual risk of malignancy in surgically excised nodules, % median (range) |
|---|---|---|
| Non diagnostic or unsatisfactory | 1–4 | 20 (9–32) |
| Benign | 0–3 | 2.5 (1–10) |
| Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) | 5–15 | 14 (6–48) |
| Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) | 15–30 | 25 (14–34) |
| Suspicious for malignancy | 60–75 | 70 (53–97) |
| Malignant | 97–99 | 99 (94–100) |

**Table 4.**
*The Bethesda system for reporting cytopathology: diagnostic categories and risk of malignancy [38].*

PTC, MTC and ATC can be diagnosed by cytopathology preoperatively. However, cytopathology cannot differentiate between FTC and follicular adenoma as histopathological findings of vascular and capsular invasion distinguish these entities.

## 9. Markers and molecular testing

FNA specimens can also be investigated for molecular markers, mutations and rearrangements to assess the risk of malignancy, prognosis and decide further management strategies in cases of indeterminate cytology.

Thyroglobulin and calcitonin in the washout fluid from FNA of cervical lymph nodes can serve as potential markers for metastatic well differentiated thyroid carcinoma and MTC respectively. TG levels of <1 ng/ml in the washout fluid is reassuring, with higher levels corresponding to increasing probability of N1 disease. This is particularly useful in cases in which lymph nodes are cystic, cases with inadequate cytological evaluation and sono-cytological discordance [1].

The 2 most common molecular testing strategies are **mutational analysis** and **gene expression analysis (GEC)**, in which genetic information can be derived from the sample obtained in the original fine-needle aspiration.

Mutational analysis involves isolating DNA from thyroid follicular cells in the specimen and performing gene sequencing. For example, RET-PTC and AKAP9/BRAF rearrangements, BRAF mutations can be associated with PTC and ATC of PTC origin. PTCs with BRAF mutation tend to be more aggressive, with greater propensity for extrathyroidal invasion and a more advanced clinical stage. FTCs are commonly associated with PAX8/PPARγ fusion in 20–50% of cases, followed by RAS mutations. The presence of markers like calcitonin and RET protein are suggestive of MTC. RET mutations are associated with fMTC, MEN2A and MEN 2B [22]. The seven gene mutation and rearrangement panel comprising of BRAF, NRAS, HRAS and KRAS point mutations, and rearrangements of RET/PTC1 and 3, and PAX8/PPARγ has a high specificity of 86–100% and a PPV of 84–100%, but poor sensitivity of 44–100%. It is being used as a **rule in test** for thyroid malignancy. However, while mutations in *RAS* genes (*HRAS*, *KRAS*, *NRAS*) are present in thyroid cancers, they are also present in nonmalignant thyroid neoplasms and in noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), and are therefore less specific. Furthermore, if no mutations are found, a thyroid malignancy with a mutation that was not assessed could still be present (~4%); therefore, mutational testing may lead to both false-negative and false-positive results, especially if *RAS* mutations are found.

The second type of molecular testing, gene expression classifier (GEC), uses a proprietary algorithm to analyse the expression of specific genes, the Afirma gene expression classifier (167 GEC), i.e. the mRNA expression of 167 genes, evaluates for the presence of a benign gene expression profile, with a high sensitivity of 92% and NPV of 93%, but low PPV and specificity of 48–53%. Hence it is used as a **rule out test** to identify benign nodules that do not require surgery. However one needs to bear in mind that nodules with a benign GEC result still have a 5% risk of malignancy [28]. MicroRNA analysis is a more recent method for molecular testing for which limited data is available.

## 10. Management

### 10.1 Toxic adenoma and toxic multinodular goitre

Patients with toxic adenoma and toxic multinodular goitre (Toxic MNG) can be managed with either radioactive iodine ablation (RAIA) or surgery with surgery

being preferred for Toxic MNG and RAIA for Toxic adenoma. For patients with toxic adenoma, the risk of treatment failure is <1% after surgical resection (ipsilateral thyroid lobectomy or isthmusectomy), whereas the risk of persistent hyperthyroidism and recurrent hyperthyroidism with radioiodine therapy is 6–18 and 3–5.5%, respectively. For patients with toxic multinodular goitre, the risk of treatment failure is <1% following surgery (near-total/total thyroidectomy), compared with 20% risk of need for retreatment following radioiodine therapy.

Radioiodine therapy may additionally be preferred in the following scenarios:

- Advanced patient age
- Comorbidities with increased surgical risk
- Small goitre size
- RAIU sufficient to allow therapy
- Previously operated or irradiated necks
- Lack of access to a high volume thyroid surgeon

Radioiodine therapy is contraindicated in pregnancy, lactation, coexisting thyroid cancer, inability to comply with radiation safety guidelines.

Surgery (near total/total thyroidectomy for multinodular goitre, ipsilateral thyroid lobectomy or isthmusectomy for toxic adenoma) can be preferred in the following scenarios:

- Symptomatic compression or large goitres >80 g
- Need for rapid correction of the thyrotoxic state
- Substernal or retrosternal extension
- Relatively low uptake of RAI
- Documented or suspected thyroid malignancy
- Large thyroid nodules, especially if >4 cm
- Coexisting hyperparathyroidism requiring surgery

In patients who are poor candidates for either therapies, long term anti-thyroid drugs (ATDs) can be considered as an alternative [39].

### 10.2 Management of thyroid nodule based on FNA findings

If a nodule is found benign on cytology, no further immediate diagnostic studies or treatment is required. Infact more than 90% of detected thyroid nodules need no intervention because they have no ultrasound features to suggest malignancy or because they are cytologically benign.

Nodules with high suspicion pattern on ultrasound can be followed up with a repeat ultrasound and FNA within 12 months, whereas nodules with low to intermediate suspicion can have a repeat ultrasound at 12–24 months. If sonographic

evidence of growth (>20% increase in atleast two nodule dimensions, with a minimal increase of 2 mm, increase in volume by 50%) or appearance of a suspicious sonographic pattern, FNA should be repeated or monitoring continued with repeat ultrasound, with repeat FNA in case of continued growth. Nodules with very low suspicion pattern can have a repeat ultrasound at ≥24 months if >1 cm, rest do not require a routine sonographic follow up. If a nodule has a second benign cytology on repeat ultrasound guided FNA, then further surveillance with ultrasound is not required. Surgery may be considered in growing nodules >4 cm, presence of compressive symptoms or cosmetic concern. There is no role of levothyroxine suppression therapy in benign thyroid nodules.

For nodules with AUS/FLUS cytology, repeat FNA and molecular testing may be used to supplement malignancy risk assessment in addition to clinical and sonographic features. Mutational testing for BRAF in AUS/FLUS samples has high specificity, but low sensitivity for cancer. Testing for the seven gene panel of mutations and rearrangements (BRAF, NRAS, KRAS, HRAS, RET/PTC1, RET/PTC3, PAX8/PPARγ) offer a significantly higher sensitivity of 63–80%. On the other hand, molecular testing using the 167 GEC (gene expression classifier) in AUS/FLUS cytology has yielded a sensitivity and NPV of 90 and 95%, respectively, but only 53% specificity and 38% PPV for cancer. If repeat FNA and molecular testing are not performed or both are inconclusive, either surveillance or diagnostic surgical excision may be carried out based on clinical and sonographic risk factors and patient preference.

If cytology is suggestive of FN/SFN, diagnostic surgical excision is the long-established standard of care. Clinical, sonographic pattern and molecular testing may be used to supplement the malignancy risk assessment. Testing for the seven gene panel of mutations in FN/SFN cytology has a sensitivity of 57–75%, specificity of 97–100%, PPV of 87–100%, NPV of 79–86%. Molecular testing with GEC is reported to have a 94% NPV, and a 37% PPV in the FN/SFN subgroup. If molecular testing is unavailable, a diagnostic surgical excision is the preferred treatment modality. No further treatment is required if the histopathology of surgical specimen is suggestive of a follicular adenoma. However, if the histopathology is suggestive of FTC, then a completion thyroidectomy may be required.

If the cytology is suspicious of papillary carcinoma (SUSP), surgical management is similar to that of malignant cytology, depending on clinical risk factors, sonographic characteristics and mutational testing if available. BRAF testing is estimated to have 36% sensitivity and 100% specificity, whereas testing with seven gene panel is reported to have 50–68% sensitivity, 86–96% specificity, 80–95% PPV and 70–75% NPV in this subgroup. On the other hand, GEC testing has a PPV (76%) similar to cytology, and a NPV of 85%, hence is not indicated in this cytological diagnosis. Molecular testing may be done if expected to alter the surgical decision making.

For a nodule with initial non diagnostic cytology, repeat FNA should be done with ultrasound guidance, and with on-site cytological evaluation if available. If the results are repeatedly non diagnostic, surgery should be considered for histopathological diagnosis in the presence of clinical and sonographic risk factors for malignancy, or growth of the nodule >20% in two dimensions detected during ultrasound surveillance.

Surgical management in cytologically indeterminate nodules (AUS/FLUS, FN/SFN, SUSP) can be either hemithyroidectomy or near total or total thyroidectomy based on clinical risk factors (nodule >4 cm, family history, history of radiation) and findings on sonography, cytology and molecular testing.

If cytology is diagnostic of a primary thyroid malignancy, then thyroid surgery is the treatment of choice. The choice of surgery depends on the stage of the

differentiated thyroid cancer. In tumours ≥4 cm, or with gross extrathyroidal invasion or clinically apparent nodal metastasis or distant metastasis, near total or total thyroidectomy is the treatment of choice. Therapeutic central compartment neck dissection should accompany the procedure in case of clinical involvement of central nodes. Therapeutic lateral neck compartmental neck dissection should be undertaken in case of biopsy proven metastatic lateral cervical lymphadenopathy. Prophylactic central compartment neck dissection can be considered in cases of papillary thyroid carcinoma with advanced primary tumour (T3/T4), or clinically involved lateral neck nodes.

For thyroid cancers >1 cm and < 4 cm, with no gross extrathyroidal invasion/nodal or distant metastasis, either lobectomy or near-total/total thyroidectomy can be considered. In tumours <1 cm, without extrathyroidal extension and nodal involvement, the initial surgical procedure should be a lobectomy, unless there are clear indications to remove the contralateral lobe. Active surveillance can be chosen in very low risk tumours like micropapillary carcinoma (tumour ≤1 cm), patients at high surgical risk or limited life expectancy [1].

Newer minimally invasive methods like percutaneous ethanol ablation, radiofrequency, laser, microwave ablation, and high-intensity focused ultrasound have been tried and may be considered for treating clinically relevant benign thyroid nodules [40]. Recurrent cystic thyroid nodules with benign cytology can be considered for percutaneous ethanol injection (PEI) or surgical excision. Ethanol acts by coagulative necrosis and small vessel thrombosis.

### 10.3 Management in specific situations: pregnancy

Thyroid nodules may enlarge slightly during pregnancy, though this does not imply malignant transformation. Patients with suppressed TSH beyond 16 weeks of pregnancy should be monitored until after delivery and cessation of lactation, followed by a radionuclide scan to assess the functional status of the nodule if TSH is still suppressed.

In euthyroid and hypothyroid patients, FNA should be done if clinically and sonographically indicated similar to non-pregnant patients. If PTC is diagnosed by cytology during pregnancy, surgery should be considered during pregnancy only if there is substantial growth (>20% increase in atleast two nodule dimensions, with a minimal increase of 2 mm, increase in volume by 50%) before 24–26 weeks of gestation, or if ultrasound reveals cervical nodes suspicious of metastatic disease. The surgery should be carried out in second trimester before 24 weeks to minimise the risk of miscarriage. If the disease remains stable by mid gestation, or diagnosed in second half of the pregnancy, surgery may be deferred until after delivery. As higher TSH levels may correlate with a more advanced stage of cancer, thyroid hormone therapy can be initiated if TSH > 2 mIU/L, with a target TSH of 0.3–2 mIU/L for the remainder of gestation.

## 11. Conclusion

Thyroid nodules pose a common clinical problem to physicians and surgeons alike. The primary concern in the evaluation of thyroid nodules is exclusion of malignancy while bearing in mind that most thyroid nodules are benign. With the advent and easy availability of high-resolution ultrasound, reliable of characterisation is possible while deciding on further testing for FNA. FNA is the single most valuable cost effective and reliable investigation for risk stratification, complemented by clinical risk factors. New molecular markers can aid in risk stratification

in nodules with indeterminate cytology. Diagnostic surgical excision can be done in these patients if associated with high risk clinical and sonographic features. Patients with malignant cytology should undergo surgery. Evidence based practices should be followed while keeping in mind patient preferences thus giving individualized precision medical care for patients with thyroid nodule.





## Author details

Madhukar Mittal*, Vanishri Ganakumar, Ravindra Shukla and Mahendra Kumar Garg
Department of Endocrinology, All India Institute of Medical Sciences, Jodhpur, India

*Address all correspondence to: mittalspace@gmail.com

## References

[1] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;**26**(1):1-133

[2] Gharib H, Papini E, Garber JR, et al. AACE/ACE/AME task force on thyroid nodules. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules-2016 update. Endocrine Practice. 2016;**22**(5):622-639

[3] Tessler FN, Middleton WD, Grant EG, et al. ACR thyroid imaging, reporting and data system (TI-RADS): White paper of the ACR TI-RADS Committee. Journal of the American College of Radiology. 2017;**14**(5):587-595

[4] Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: The EU-TIRADS. European Thyroid Journal. 2017;**6**(5):225-237

[5] Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Annals of Internal Medicine. 1968; **69**(3):537-540

[6] Bartolotta TV, Midiri M, Runza G, Galia M, Taibbi A, Damiani L, et al. Incidentally discovered thyroid nodules: Incidence, and greyscale and colour Doppler pattern in an adult population screened by real-time compound spatial sonography. La Radiologia Medica. 2006;**111**(7):989-998

[7] Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Practice & Research. Clinical Endocrinology & Metabolism. 2008;**22**(6):901-911

[8] Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. The Journal of Clinical Endocrinology and Metabolism. 1955;**15**(10):1270-1280

[9] Popoveniuc G, Jonklaas J. Thyroid nodules. The Medical Clinics of North America. 2012;**96**(2):329-349

[10] Lio S, Napolitano G, Marinuzzi G, Monaco F. Role of smoking in goiter morphology and thyrotropin response to TRH in untreated goitrous women. Journal of Endocrinological Investigation. 1989;**12**(2):93-97

[11] Wang N, Fang H, Fu C, Huang P, Su M, Jiang F, et al. Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficient areas: An observational study. BMJ Open. 1 October 2017;**7**(10):e016706

[12] de Sousa PAM, Vaisman M, Carneiro JRI, Guimarães L, Freitas H, Pinheiro MFC, et al. Prevalence of goiter and thyroid nodular disease in patients with class III obesity. Arquivos Brasileiros de Endocrinologia e Metabologia. 2013;**57**(2):120-125

[13] Völzke H, Friedrich N, Schipf S, Haring R, Lüdemann J, Nauck M, et al. Association between serum insulin-like growth factor-I levels and thyroid disorders in a population-based study. The Journal of Clinical Endocrinology and Metabolism. 2007;**92**(10):4039-4045

[14] Hsiao PJ, Tsai JH. Increased insulin-like growth factor-1 receptors in thyroid tissues of graves' disease. Journal of

the Formosan Medical Association. 1994;**93**(11-12):925-932

[15] Liu Y-J, Qiang W, Liu X-J, Xu L, Guo H, Wu L-P, et al. Association of insulin-like growth factor-1 with thyroid nodules. Oncology Letters. Nov 2011;**2**(6):1297-1301

[16] Risk Factors for Goiter and Thyroid Nodules|Thyroid [Internet]. 2019. Available from: https://www.liebertpub.com/doi/pdf/10.1089/105072502761016502

[17] Senyurek Giles Y, Fatih T, Harika B, Yersu K, Tarik T, Serdar T. The risk factors for malignancy in surgically treated patients for graves' disease, toxic multinodular goiter, and toxic adenoma. Surgery. 2008;**144**(6):1028-1037

[18] Kim WB, Han S-M, Kim TY, Nam-Goong IS, Gong G, Lee HK, et al. Ultrasonographic screening for detection of thyroid cancer in patients with graves' disease. Clinical Endocrinology. 2004;**60**(6):719-725

[19] Bibbins-Domingo K, Grossman DC, Curry SJ, Barry MJ, Davidson KW, Doubeni CA, et al. Screening for thyroid cancer: US preventive services task force recommendation statement. Journal of the American Medical Association. 2017;**317**(18):1882-1887

[20] Hegedüs L. Clinical practice. The thyroid nodule. The New England Journal of Medicine. 2004;**351**(17):1764-1771

[21] Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, Lupo L, et al. Cancer risk in patients with cold thyroid nodules: Relevance of iodine intake, sex, age, and multinodularity. The American Journal of Medicine. 1992;**93**(4):363-369

[22] Niedziela M. Thyroid nodules. Best Practice & Research. Clinical Endocrinology & Metabolism. 2014;**28**(2):245-277

[23] Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. The Journal of Clinical Endocrinology and Metabolism. 2008;**93**(3):809-814

[24] Golbert L, de Cristo AP, Faccin CS, Farenzena M, Folgierini H, Graudenz MS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. PLoS One. 2017;**12**(11):e0188123

[25] Reschini E, Ferrari C, Castellani M, Matheoud R, Paracchi A, Marotta G, et al. The trapping-only nodules of the thyroid gland: Prevalence study. Thyroid. 2006;**16**(8):757-762

[26] Werk EE, Vernon BM, Gonzalez JJ, Ungaro PC, McCoy RC. Cancer in thyroid nodules. A community hospital survey. Archives of Internal Medicine. 1984;**144**(3):474-476

[27] Belfiore A, Giuffrida D, La Rosa GL, Ippolito O, Russo G, Fiumara A, et al. High frequency of cancer in cold thyroid nodules occurring at young age. Acta Endocrinologica. 1989;**121**(2):197-202

[28] Lin J-D, Chao T-C, Huang B-Y, Chen S-T, Chang H-Y, Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid. 2005;**15**(7):708-717

[29] Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. Clinical Diabetes and Endocrinology. 1 December 2016;**2**(1):17

[30] Leboulleux S, Girard E, Rose M, Travagli JP, Sabbah N, Caillou B, et al. Ultrasound criteria of malignancy

for cervical lymph nodes in patients followed up for differentiated thyroid cancer. The Journal of Clinical Endocrinology and Metabolism. 2007;**92**(9):3590-3594

[31] Yeh MW, Bauer AJ, Bernet VA, Ferris RL, Loevner LA, Mandel SJ, et al. American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. Thyroid. 2015;**25**(1):3-14

[32] Moon HJ, Sung JM, Kim E-K, Yoon JH, Youk JH, Kwak JY. Diagnostic performance of gray-scale US and elastography in solid thyroid nodules. Radiology. 2012;**262**(3):1002-1013

[33] Lesnik D, Cunnane ME, Zurakowski D, Acar GO, Ecevit C, Mace A, et al. Papillary thyroid carcinoma nodal surgery directed by a preoperative radiographic map utilizing CT scan and ultrasound in all primary and reoperative patients. Head & Neck. 2014;**36**(2):191-202

[34] Suh CH, Baek JH, Choi YJ, Lee JH. Performance of CT in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid cancer: A systematic review and meta-analysis. AJNR. American Journal of Neuroradiology. 2017;**38**(1):154-161

[35] Padovani RP, Kasamatsu TS, Nakabashi CCD, Camacho CP, Andreoni DM, Malouf EZ, et al. One month is sufficient for urinary iodine to return to its baseline value after the use of water-soluble iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy. Thyroid. 2012;**22**(9):926-930

[36] Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. The Journal of Clinical Endocrinology and Metabolism. 2009;**94**(5):1748-1751

[37] Hamberger B, Gharib H, Melton LJ, Goellner JR, Zinsmeister AR. Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. The American Journal of Medicine. 1982;**73**(3):381-384

[38] Cibas ES, Ali SZ. NCI thyroid FNA state of the science conference. The Bethesda system for reporting thyroid cytopathology. American Journal of Clinical Pathology. 2009;**132**(5):658-665

[39] Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;**26**(10):1343-1421

[40] Papini E, Pacella CM, Misischi I, Guglielmi R, Bizzarri G, Døssing H, et al. The advent of ultrasound-guided ablation techniques in nodular thyroid disease: Towards a patient-tailored approach. Best Practice & Research. Clinical Endocrinology & Metabolism. 2014;**28**(4):601-618