Current Diagnosis and Management of Thyroid Nodules

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ABSTRAK

Nodul tiroid sangat umum diketemukan. Walaupun banyak kasus nodul tiroid yang didapati dari pemeriksan fisik, ternyata banyak juga yang diketemukan secara tidak sengaja pada saat pemeriksaan radiologi. Sepuluh sampai 15% dari nodul tiroid merupakan keganasan tiroid. Klinisi seperti internis/endokrinologis bertugas mengklasifikasikan nodul tersebut, menstratifikasikan risiko karsinoma tiroid, melakukan upaya diagnostik, memberikan terapi medis / non-bedah, memilah kasus yang memerlukan operasi dan melakukan follow-up jangka panjang. Artikel ini merupakan ulasan terkini dari upaya diagnostik dan terapi nodul tiroid, fokus pada algoritme penatalaksaan nodul tiroid dan karsinoma tiroid berdiferensiasi baik dari American Thyroid Association yang terbaru.

Kata kunci: *nodul tiroid, karsinoma tiroid, penatalaksanaan, terapi.*

ABSTRACT

Thyroid nodules are frequently found. Although they are often palpable, many are found incidentally during unrelated radiographic studies. Ten to 15% of thyroid nodules represents thyroid malignancy. Clinician suc as an internist/endocrinologist have to classify the nodule, stratify the risk of thyroid cancer, performed a diagnostic work-up, provide medical / non-surgical therapy, select candidates for surgery and provide appropriate follow-up that should last a lifetime. This article provide an up-date review of diagnostic approach and management of thyroid nodules, focusing on current algorithm in lights of the most recent published American Thyroid Association thyroid nodule and differentiated thyroid cancer management guidelines.

Keywords: *thyroid nodule, thyroid cancer, management, therapy.*

INTRODUCTION

Nodules in the thyroid gland, whether solitary or multiple, are very common in clinical practice. Thyroid nodules are detected in approximately 5-7% of an adult population upon physical examination. Since modern ultrasound (US) techniques can detect small nodules, the frequency of thyroid nodules has been reported as high as 67% in unselected subjects.[1] Furthermore, thyroid nodules continue to be diagnosed with great frequency, probably because of widespread use of various imaging procedures (computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), etc.) that detect thyroid nodules "incidentally".[2] Thyroid nodules are clinically important because they can represents thyroid cancer, which occurs

approximately 10-15% of nodules.[3] Other consideration are the risk of thyroid dysfunction (autonomous adenoma and toxic multinodular goiter), compressive symptoms and some cosmetic concern. The main concern of patients and physicians is to diagnosed the suspected cancers as rapidly and cost effectively as possible and reduce unnecessary thyroid surgery.[4]

This article reviews the current thinking regarding work up of *de novo* thyroid nodule. We highlight the most recent 2015 publication of the American Thyroid Association's (ATA) management guidelines on thyroid nodules and differentiated thyroid cancer.[5]

ETIOLOGY OF THYROID NODULES

As defined by the ATA's task force on the management of thyroid nodules and differentiated thyroid cancer,[5] a thyroid nodule can defined as a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding parenchyma. It may be solitary, multiple, cystic, or solid, and may or not be functional; accordingly, the exact morphological characteristics, thyroid functional status and pathological evaluation need to be assessed.[6] A simple way to classify thyroid nodules is to describe them as non-neoplastic and neoplastic. Neoplastic thyroid nodules can be benign or malignant.[7] The differential diagnosis of the thyroid nodule are listed in **Table 1**.

Table 1. Clinical and pathological classification of thyroid nodules

Non-neoplastic nodules
- Hyperplastic
- Spontaneous
- Compensatory after partial thyroidectomy
- Inflammatory
- Acute bacterial thyroiditis
- Subacute thyroiditis
- Lymphocytic (Hashimoto's) thyroiditis
Benign neoplasms
- Non-functioning (cold nodules)
- Solid (or mixed): adenoma
- Cystic
- Functioning (hot nodules)
- Adenoma
Malignant neoplasms
- Primary carcinoma
- Papillary carcinoma
- Follicular carcinoma
- Anaplastic carcinoma
- Medullary carcinoma
- Thyroid lymphoma
- Thyroid metastasis from other primaries

DIAGNOSIS APPROACH OF THYROID NODULES: THYROID CANCER OR NOT?

The most important point in the diagnostic approach is to look for data indicating malignancy in the findings obtained through the patient's history, physical examination, laboratory test, and imaging techniques (**Table 2**).[8] There are four essential modalities: clinical evaluation, thyroid function test, thyroid US, the FNA,[4,9] and they will be discussed briefly.

Table 2. Diagnostic methods used in the evaluation of thyroid nodule

Clinical examination
- History of benign thyroid disease
- History of head and neck irradiation
- Family history of thyroid cancer
- Physical examination
Laboratory investigations
- TSH
- Anti-TPO/anti-Tg antibody
- Serum calcitonin (selected cases)
Imaging methods
- Thyroid ultrasonography
- Radionuclide scanning (selective use)
- CT, MRI, PET scan (selective use)
Cytologic or histologic examination
- Fine-needle aspiration
- Large-needle biopsy
- Core-needle biopsy

Abbreviations: TSH, thyroid stimulating hormone; Anti-TPO, antibody antithyroglobulin antibody; Anti-Tg, antithyroglobulin antibody; CT, compute tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Clinical Examination

Most thyroid nodules are asymptomatic and discovered by the patient or by physician during neck palpation. The features (sign and symptoms) of thyroid malignancy are shown in **Table 3** that can be found in various settings, including during

Tabel 3. Features suggestive of increased potential of malignancy in patient with thyroid nodule

Patient history or characteristics	Physical examination	Findings seen on imaging (in case of incidentaloma)
Family history of MEN, MTC, and PTC	Firm nodule Nodule fixed to adjacent structures	Suspicious ultrasound features: microcalcification, intranodal hypervascularity (evaluated by Doppler), hypoechogenicity, nodule with irregular border, etc.
History of head and neck irradiation	Large nodules (> 4cm)	Cervical lymphadenopathy
History of Hodgkin and non-Hodgkin lymphoma	Growth of nodule, especially during L-thyroxine therapy suppression therapy	Focal uptake on 18FDG-PET scan or 99mTcMIBI
Age < 20 or > 70 years	Symptoms of compression: hoarseness, dysphagia, dysphonia, dyspnea, cough	
Male sex	Abnormal cervical lymphadenopathy	
	Paralysis of vocal cords	

Abbreviations: MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; ^{18}FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; 99mTcMIBI, 99mTc-2-methoxy-isobutylisonitrile. Source: Popoveniuc G and Jonklaas J. Med Clin North Am 2012

routine physical examination or nodule found incidentally on imaging procedure.[5,9,10]

Laboratory Investigations

Thyroid Stimulating Hormone (TSH) – thyroid peroxidase antibodies. After obtaining a history and physical examination, a decision will be made about whether to further pursue workup. The first step, if that workup is to be undertaken, is to obtain a result of TSH.[5] A finding of suppressed TSH concentration suggest the need for determination of serum free thyroxine (fT4) and free triidothyronine (fT3)[4,6,11] and thyroid scintigraphy (if available) to visualize areas of high (hot nodules) and low (cold nodules) iodine uptake.[5] Functioning nodules has little possibility of being malignant; hence, no additional cytologic evaluation is necessary except in context of multiple thyroid nodules.[6] In cases of normal or high serum TSH, diagnostic US should be performed. A normal TSH should be followed by needle-biopsy if appropriate, and a high TSH should get a work-up for hypothyroidism (anti thyroid peroxidase antibodies should also be obtained to confirm Hashimoto's thyroiditis) in addition to needle biopsy when indicated.[5,11]

Other laboratory: Antithyroglobulin and calcitonin. The essential of thyroglobulin combined with anti-thyroglobulin antibody titering as they are markers for recurrence of disease in the follow-up of thyroid cancer after total thyroidectomy and radioactive ablation therapy.[4,9-11] Measurement of antithyroid antibody testing (anti-thyroid peroxidase and anti-thyroglobulin) is not necessary in the routine work-up of a thyroid nodule.[5] One additional study that merits mentioning is calcitonin. Calcitonin is a sensitive and specific tumor marker used in the diagnosis, surveillance, and prognosis of medullary thyroid carcinoma (MTC).[11] In the presence of a family history of medullary carcinoma or multiple endocrine neoplasia syndromes, the presence of nodule should alert the possibility of MTC, thus allow early radical surgery. Routine serum calcitonin titering is not recommended in the ATA's guidelines.[5]

Imaging Methods

Neck palpation is very imprecise with regard to the determination of thyroid nodule morphology and size.[3,6,9,10] For this reason, imaging methods are increasingly used, although no imaging methods can accurately differentiate benign and malignant nodules. To some extent, morphological characterization including thyroid cancer risk stratification of the lesion lies on imaging modalities.[5,8]

Ultrasonography (US). US examination is highly accurate and sensitive in evaluating thyroid nodules.[5,12,13] US examination was able to detect thyroid incidentaloma which cannot be obtained by physical examination. Thyroid US is the first choice of imaging studies for thyroid gland evaluation. Indication of US examination on thyroid nodules are: a) all types of thyroid nodules, b) thyroid nodules with the history of neck radiation, and c) thyroid nodules with the history of familial thyroid cancer, multiple endocrine neoplasia (MEN) type 2, even if the gland appears normal by palpation.[5] Several ultrasound findings have been found to be associated with malignancy among patients brought to surgery after FNA. A solid nodule, hypoechogenicity, microcalcifications, irregular contours, subcapsular localization, invasive growth, multifocal lesion, increased nodule blood flow on Doppler (when TSH is normal) and suspicious regional lymphadenopathy on US indicate malignancy.[14] A ratio of the anteroposterior diameter of the nodule to the transverse diameter (AP/T) >1 indicated malignancy.[11] Nodules that are cystic, isoechoic, have regular boundaries, lack calcification and show no invasive growth usually considered benign.[13]

The number of nodules and their size are not predictive of malignancy, as a nodule smaller than 1 cm is as likely as a larger nodule to harbor neoplastic cells in the presence of suspicious US features. The ATA 2015 recommendation suggest nodules as small as 1 cm might be biopsied and should be followed based on risk factors (**Table 4**).[5] Large nodules also merit discussion; some nodules are so large it has been asserted that they should be surgically removed without taking the extra step of biopsy. In an article published in 2007,15 among patients brought to surgery who had been diagnosed with nodules greater than 4 cm, FNA results were frequently false negative. They often eventually affect speech and swallow function due to size, and for this reason, large nodules (~4 cm or greater) could be offered for surgical intervention because they are less accurately assessed by FNA.

Table 4. Recommended size thresholds for consideration of FNA as part of evaluation of a thyroid nodule.[5]

Nodule sonographic or clinical features	Nodule threshold size for FNA	Grade of Recommendation[a]
High-risk history[b]		
- Nodule WITH suspicious US features[c]	≥ 1 cm	A
- Nodule WITHOUT suspicious US features[c]	≥ 1 cm	I
Abnormal cervical lymph nodes	All[d]	A
Microcalcifications present in nodule	≥ 1 cm	B
Solid nodule		
- AND hypoechoic	> 1 cm	B
- AND iso- or hyperechoic	≥ 1-1.5 cm	C
Mixed cystic-solid nodule		
- WITH any suspicious US features[c]	≥ 1.5-2.0 cm	B
- WITHOUT any suspicious US features[c]	≥ 2.0 cm	C
Spongiform nodule	≥ 2.0 cm	C
Purely cystic nodule	FNAC not indicated[e]	E

[a] Explanation for recommendation: A, strongly recommends based on good evidence; B, recommends, based of fair evidence; C, recommends, based on expert opinion; E, recommends against based on fair evidence; I, neither recommends nor against, evidence insufficient.
[b] High-risk history: History of thyroid cancer in first degree relative, history of external beam radiation, exposure to ionizing radiation, prior hemithyroidectomy with discovery of thyroid cancer, 18FDG avidity on PET scanning, MEN2/FMTC-associated RET proto-oncogene mutation, calcitonin >100 pg/mL.
[c] Suspicious features: see ultrasonography section of this issue.
[d] FNA cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule.
[e] Unless indicated as therapeutic modality.

Thyroid Scintigraphy. Scintigraphy of the thyroid gland utilize one of the radioisotopes of iodine (usually ^{123}I) or technetium-99 pertechnetate (^{99}Tc).[3-6,9,10] Its use is recommended in patients with suppressed TSH to document whether a nodule is functioning or not, before needle biopsy.[16] Accordingly, a nodule is considered functioning or "hot" (i.e. has tracer uptake greater than the surrounding normal thyroid), isofunctioning or "warm" (i.e. has tracer uptake equal to the surrounding thyroid), and non-functioning or "cold" (i.e. has uptake less than the surrounding thyroid tissue). Scintigraphy provides functional rather than morphological information, contrary to US.[17] Scintigraphy has been largely replaced by US but still has at least 2 roles: identifying hyperfunctioning nodules when a low TSH is found on initial testing, and to a limited extent, determining which nodule(s) to sample in patients with multiple nodules.[6,16,17] Hot nodules do not require FNA, as they rarely harbor cancer.[6,16] It is the cold nodule that warrants FNA, depending on size and US characteristics. For the purpose of biopsy decisions, indeterminate nodules should be treated as though they are nonfunctioning, and subjects to cytological analysis.[5,16]

Cytology and Histology Examination

Fine-needle aspiration and its indication. This is the most important study, which should never be left out in the presence of a thyroid nodule. There are 3 main considerations to categorizing and determining whether the nodule should undergo FNA: patient's history, nodule size, and US features (**Table 2**, ATA guidelines for FNA threshold).[5] In the context of a palpable nodule, FNA may be performed with or without US guidance.[18] It is suggested that US-FNA be performed in: 1) nonpalpable nodules larger than 1 cm, 2) palpable nodule smaller than 1.5 cm, 3) deeply found nodules, 4) nodules in close to blood vessels, 5) nodules after a nondiagnostic conventional FNAC, 6) cystic or mixed nodules, especially if a previous conventional FNA was nondiagnostic, and 7) coexistence of nonpalpable lymphadenopathy. For nodules fall outside the criteria for biopsy, it is reasonable to do interval thyroid US follow-up.[5]

MANAGEMENT APPROACH

Despite many investigation options available to the clinicians, the management of thyroid nodule essentially depends on the FNA results.[5] The possible reports are benign, malignant, suspicious malignancy, atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm or suspisious for a follicular neoplasm (FN/SFN), and non-diagnostic.[19] Beside cytological diagnosis, the treatment plan may depend on the patient's age and gender and the characteristics of the nodule (size, consistency, activity, and number), and whether it is functioning or not (**Figure 1**).[4,5,9,10] Treatment modalities are shown in **Table 5**.

Asymptomatic benign euthyroid nodules need only watchful follow-up with annual or biannual US and TSH testing.[5] Nevertheless, on some occasion, benign thyroid nodules do require therapeutic intervention, especially when they grow large and when they cause obstructive symptoms.[3,7,10,20] Any type of malignancy, or when malignancy cannot be ruled out, indicated the need for surgical resection. The extent of surgery depends on the type of tumor. Simple hemithyroidectomy may be recommended as the initial step for follicular neoplasm or as the definitive treatment for a small, isolated papillary carcinoma if no other risk factors are present.[20] All other thyroid malignancy deserve total thyroidectomy with complementary local node resection. If the histology of the follicular neoplasm confirms the presence of carcinoma, the a total thyroidectomy should be completed.[5,7,20]

Surgical Management of Thyroid Nodules

When there is malignant or suspicious cytologic features and/or symptoms due to the nodule, surgery is often recommended, especially for younger patients and in case in which there are large nodules.[8] The preferred operation is a unilateral removal of the affected node.[5,7,20] Complications include temporary and permanent unilateral vocal cord paralysis (1-2 and 0.5-1.0%, respectively), temporary and permanent hypocalcemia (1.0 and 0.5%, respectively), and hematomas and infections

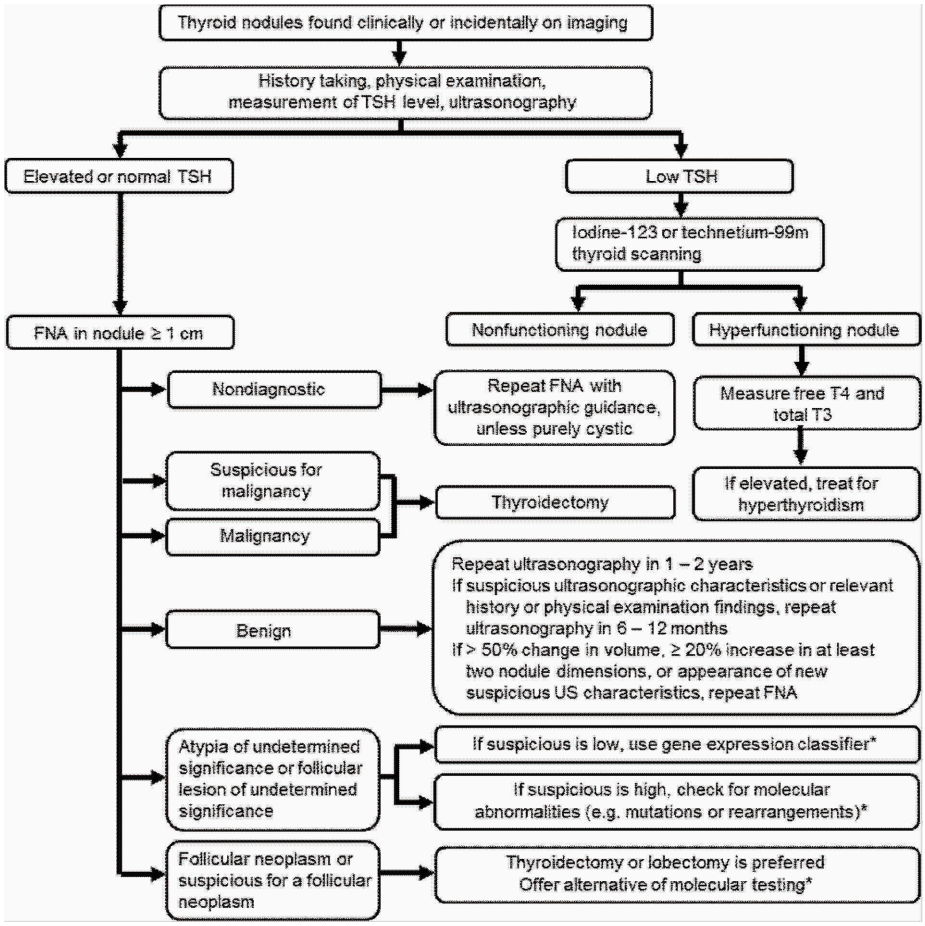

Figure 1. Algorithm for evaluation and treament of thyroid nodules. Source: Burman KD and Wartofsky L. N Engl J Med 2015. * Molecular abnormalities are not subjects of this article.

(0.5 and 0.3%, respectively).[7] The risk of complications increases with the extent of operation. In the patient with normal thyroid function postoperatively, there is no indication for routine L-thyroxine treatment since this does not seem to hinder thyroid growth in the long term, at least in iodine-sufficient regions.[20,21] Although an option, surgery is rarely used in the hyperthyroid patient with a toxic nodule. Radioactive iodine treatment is the preferred treatment for "hot" nodule.[4,6]

Benign cytology: Surgical treatment is indicated for some benign lesions, either single or associated with multinodular goiter, if they are large (>4 cm in diameter), presence of signs and symptoms of compression, cause discomfort, if there are cosmetic concern.[20] Recurrent cyst after therapeutic aspirations of the fluid may have indication for surgery becausae these lesion may have malignant cells in up to 10% of cases. All the other benign nodules are candidate for medical therapy.[21] The patients with benign cytology and low risk factors may still need follow up for a further 12 – 24 months considering 5% false negative FNA results. US-FNA need to be repeated if nodule grows significantly. Growth of nodule is considered significant with an increase in diameter of 20% or more with a minimum increase of 2 mm.[5] Benign cytology in a patient with high risk factors as mentioned in **Table 3** may need diagnostic lobectomy. Patients with a dominant nodule in a multi nodular goiter with compressive symptoms need total thyroidectomy and post-operative L-thyroxine replacement therapy. The other indication for surgery in benign thyroid nodules include the presence of a toxic adenoma or a toxic multinodular goiter.[9,10,20] In the event of thyrotoxicosis, surgery must be performed after restoration of a normal thyroid function by

Table 5. Advantages and disadvantages of the established treatment options for the thyoid nodule

Treatment	Advantages	Disadvantages
Levothyroxine	Outpatient	Low efficiency
	Low cost	Lifelong treatment
	May slow nodule growth	Regrowth after cassation
	Possibly prevents new nodule formation	Adverse effects on bone and heart
		Not feasible with TSH suppressed
Radioiodine	Outpatient	Operator dependency
	Low cost	Contraseptives needed in fertile women
		Side effect
		- Radiation thyroiditis
		- Graves' disease
		- Hypothyroidism
		- Long-term cancer risk unknown
Ethanol injection	Outpatient	Repeat injection needed
	Relatively low cost	Low efficacy in large nodules
	Thyroid function preserved	
		Side effects
		- Pain
		- Transient dysphonia
		- Thyroiditis
		- Extranodular fibrosis
		- Complicates subsequent cytological interpretation
Surgery	Prompt relief of symptoms	Inpatient
	Nodule abplation	High cost
	Definite diagnosis	Anesthesiological risk
		Surgical risk
		- Vocal cord paralysis
		- Hypoparathyroidism
		- Hypothyroidism
		- Bleeding and infection
		- Scar

adequate preparation with antithyroid drugs to avoid thyroid crisis complication.[4]

Malignant Cytology

In malignant cytology or suspicious cases, total thyroidectomy is the treatment of choice to achieve loco-regional control in most patients. This also enables a patient with thyroid cancer to undertake post-operative radioiodine (I131) ablation, to treat the microscopic disease.[8,20,22] The only exception could be a papillary microcarcinoma (<1 cm) of thyroid in the absence of local invasion. In this situation, the ATA suggest lobectomy.[5] This article focuses on the investigation and treatment of thyroid nodule, and therefore, detailed analysis of treatment of all thyroid cancer is beyond the scope of our discussion. However, general management guideline of differentiated thyroid cancer is outlined below.

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer accounting for 80–85% of thyroid cancers.[3,7-10] It is associated with good prognosis and the cancers more than 1 cm are best managed with total thyroidectomy.[5,8] Completion thyroidectomy is indicated in patients who undergone prior diagnostic

lobectomy and are found on final pathology to have PTC that is larger than 1 cm.[23] The completion of thyroidectomy should generally performed within 6 months of the original procedure in order to minimize the risk of lymph node metastasis. Routine central compartment dissection is controversial, but it is estimated that up to 50% of patients have neck metastasis at the time of diagnosis.[24] Currently, there is no prospective, randomized trials comparing prophylactic to therapeutic central lymph node dissection. Current practice guidelines from the ATA recommend therapeutic central or lateral lymph node clearance in PTC for clinically positive nodes. But guidelines regarding prophylactic neck dissection are less clear. The prophylactic neck dissection may be performed parpticularly in patients with T3 or T4 tumors, and dissection "may be reasonably avoided" for patients with T1 or T2 disease.[5] Currently, lifelong TSH suppression is advocated though the degree of suppression and its length are the subjects of review.[8,23]

Follicular thyroid cancer (FTC) are diagnosed on histology based on capsular/vascular invasion and constitute 10% of thyroid malignancy.[3,7-10] Routine FNA cytology are generally not able to be discerned this histologic features from follicular neoplasm (their benign counterpart). Thus, AUS/FLUS and FN/SFN need diagnostic lobectomy to confirm follicular carcinoma.[9,19,20] If this is proven on histology, the patient needs completion thyroidectomy later.[5,22] The role of intra-operative frozen section of thyroid these patients generates considerable controversies. A study involving 564 patients with thyroid tumors examined the frozen section in 70% of the patients. Based on this study, it was concluded that intra-operative frozen section on thyroid tumors adds very little to surgical management.[25] Follicular cancer spreads hematogenously as compared to PTC which mainly spreads by the lymphatic system. Therefore routine central compartment clearance is not indicated unless there are positive neck nodes on US and FNA. Radioactive I^{131} ablation and lifelong TSH suppression therapy with follow-up as for PTC is required.[8,23] Post-operative treatment with radioactive I^{131} is primarily applied for three reasons. First, RAI ablates or eliminates any remaining normal thyroid tissue and facilitates the specificity of thyroglobulin as a tumor markers in long-term surveillance. Second, RAI serves as an adjuvant treatment of intermediate-risk patients to destroy the remaining occult small foci of well-differentiated thyroid carcinoma and potentiating a decrease in risk of recurrence. Finnaly, RAI may be administered in a therapeutic fashion for those high-risk patients with macroscopic residual disease (remnant ablation) or distant metastatic disease.[22,23] The 2015 ATA recommendation currently recommends the use of RAI postoperatively in patients with T3, T4, or M1 disease.[5]

Nonsurgical Management of Thyroid Nodules

Levothyroxine therapy. Although on the decline, it is still common practice to used thyroid suppression with levothyroxine (L-thyroxine) in the management of solid thyroid nodule in euthyroid patients.[26] The aim is to shrink existing nodules, considered to be a favorable sign indicating that the nodule is benign.[3] However, the effectiveness of medical treatment of benign nodule(s) with L-TSH suppressive doses remains controversial.[5] It seems that young healthy patients with small and solid nodules from iodine-deficient areas could benefit the most.[21] Approximately 20% of solitary solid nodules actually regress as a result of L-thyroxine therapy, and cessation of therapy leads to rapid regrowth. On average, long-term therapy is without significant nodule-reducing effect. Growth can be suppressed or slowed, and the formation of new nodules may be prevented. However, this necessitates that serum TSH is suppressed to subnormal values (treat to TSH target 0.1 – 0.45 mIU/mL), which may have adverse effects.[21] This degree of TSH suppression, called mild or subclinical hyperthyroidism, is associated with an increased risk of atrial fibrillation, other cardiac side effects, and reduced bone density, potentially leading to osteoporosis.[26] The use of L-thyroxine therapy should be avoided for large nodule or long standing goiters, particularly of the TSH value is less than 0.5 mIU/mL, postmenopausal women or person older than 60 years, patients

who have osteoporosis, cardiovascular disease or systemic illnesses.[21,26] Also, L-thyroxine therapy has no effect in the cystic nodule and in patients with spontaneously low serum TSH with or without elevated thyroid hormone levels.[21] For these reasons, its use is questionable; at most, it can be used in younger patients with small nodules, in whom treatment is least necessary. Routine L-thyroxine suppressive therapy is no longer recommended for cytologically benign nodules.[5]

Radioactive iodine. If the patient has hyperthyroidism (toxic nodule), antithyroid drugs (propylthiouracyl or methimazole) can normalize thyroid function but disease recurrence is the rule when medication is stopped.[4] With the exception of few patients who have a large nodule, in which case that surgery indicated, radioactive iodine is the treatment of choice. This is also the case for the clinically euthyroid patient with functioning ("hot") nodule, in whom treatment may be dictated by the nodule size, which may cause compression or cosmetic disturbance.[6] In addition, radioactive iodine treatment is used to prevent hyperthyroidism (annual risk of approximately 4%). Pretreatment with recombinant human TSH offers the prospect that radioiodine treatment of nontoxic nodular goiters can be simplified and improved, however, more information about this strategy is needed.[27] A cure rate (i.e. normalization of thyroid function and the appearance on a thyroid isotope scintigraphy) of 70% is seen, and the nodule shrinks 30-60% following a single dose of radioactive iodine.[22] Side effects are few, with rare cases of radiation thyroiditis and transition to Graves' disease. The risk of hypothyroidism is approximately 10% after 5 years and unrelated to the dose of radioactivity.[27] The long-term risk of malignancy is unknown but considered negligible. Radioactive iodine has no effect on the nonfunctioning (cold) nodule, whether solid or cystic. In the future, the possibility of stimulation with recombinant human TSH before radioactive iodine treatment may lead to an increased iodine uptake and also lead to an increased iodine uptake and also an effect in the solid and cold nodule.[22]

In Situ Destruction of Thyroid Nodules

Percutaneous Ethanol Injection (PEI). US-guided PEI into nodules (especially the symptomatic cystic nodules) has been proposed as a valid, safe, well tolerated, inexpensive alternative therapputic method for in situ ablation of benign thyroid nodule.[21] Ethanol (70-100%) causes local small vessel thrombosis and coagulative necrosis, leading to fibrosis and permanent tissue ablation. It has been used both autonomously functioning thyroid nodules and nonfunctioning thyroid nodules, whether solid or cystic. In solitary nodule, nonfunctioning thyroid nodules, approximately 50% of patients are relieved of their clinical symptoms based on a 50-90% nodule volume reduction in thyroid nodules larger than 30 gr. Additional injections have little effect.[28] It is an option for patients who do not wish to undergo radioiodine treatment or surgery.[5] However, it often necessitates repeat treatment to obtain complete cure. However, because of the frequent, although transient, side effects (particularly local pain), PEI should be limited to highly selected nodules that are easily accessible to palpation in patients refusing I^{131} and surgery.[5,21] This procedure, often used in Italian centers, is not a routine option, should still be classified as experimental, and requires the special technical skill that can be obtained only at center familiar with interventional ultrasound.[29]

Intertitial Laser Photocoagulation (IL). Ultrasound-guided ILP has been used as a norsurgical alternative in the treatment of benign, solitary, solid (both "hot" or "cold" nodule) in patients who cannot (or will not) undergo surgery.[30] One treatment lasting approximately 10 min resulted in a 40% nodule reduction and significant pressure symptoms reduction. These results are similar to those obtained using ethanol therapy. The fact that the spread of energy with a laser (thermal destruction) can be controlled, as opposed to chemical destruction by injection of ethanol, may favor laser therapy in then long-term.[21]

Radiofrequency ablation. Radiofrequency ablation (RFA) is a minimally invasive treatment for certain type of benign thyroid nodules

when surgery is not an option. RFA therapy has mainly been aimed at decreasing pressure symptoms, improving cosmetic results as well as resolving thyrotoxic status in "hot" nodules. For "cold" nodules, the efficacy of RFA has mainly been evaluated in terms of reduction of nodule volume, pressure symptoms, and cosmetic symptoms.[31] A recent study by Korean group[32] who compared the efficacy and safety of surgery and RFA reported that both are effective treatment in benign thyroid nodules. After RAI, the nodal volume decreased significantly and give more benefit in terms of lesser post-operative complication, preservation of thyroid function and fewer hospitalization days, compared to surgery. Currently, no explanation how international guidelines recommends RFA for benign thyoid nodule.[5]

FOLLOW-UP

The follow-up of benign euthyroid thyroid nodules depends on the clinical, US and cytological characteristics described earlier.[5] Usually, thyroid nodule require reevaluation every 12 to 24 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 within 1 to 2 months.[10] 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 lesion also grow larger, but a repeat FNA should be considered. The same recommendation is valid if new clinical or US features of malignancy appear.[5,9] Thyroglobulin level monitoring is used a screen for cancer recurrence in patients with differentiated thyroid cancer after total thyroidectomy and radioactive iodine ablation.[5,7] Thyroid function should also be regularly investigated (usualy yearly) in those patients who have been treated with ablative options (surgery or I^{131}).[23] This is generally evaluated by a serum TSH determination. If hypothyroidism shows up, treatment should be started with L-thyroxine replacement therapy, which itself also requires annual follow-up. Post-surgical thyroid US is useful in monitoring the evolution of the remaining gland.

CONCLUSION

Diagnosis and therapy of thyroid nodules is highly determinate by early evaluation, clinical criteria using TSH measurement, US and FNA as initial test. They should be practical, efficient and cost-effective. In multinodular thyroid, FNA biopsy can be restricted to the dominant nodule with special preference to high suspicious pattern nodule on imaging. Surgery is required if malignant or suspicious cytology is reported. Rapid growth and increasing pressure effects and cosmetic reason are also indication for surgery. Simple observation and L-thyroxine suppression are acceptable management option with presumably benign thyroid nodules. Ablation of thyroid nodules (ethanol injection and laser photocoagulation) have been used for in situ destruction of benign solid nodules. Radiofrequency ablation (RFA) therapy is currently viewed as experimental therapeutic method. Radioiodine therapy (RAI) may be used for the management in selected patients. For indeterminate cytology, diagnostic surgery may needed to exclude malignancy.

Declaration of interest: The author declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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