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Thyroid Nodule; Updates Managements: A Review Literature

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Abstract

Thyroid nodules are a common finding. Although they are frequently perceptible, many are discovered by chance during unrelated imaging examinations. Thyroid cancer accounts for 10% to 15% of thyroid nodules. An internist/endocrinologist must identify the nodule, stratify the risk of thyroid cancer, do a diagnostic work-up, offer medical/non-surgical therapy, choose candidates for surgery, and provide adequate follow-up that should last a lifetime. This article provides an up-to-date assessment of the diagnostic method and management of thyroid nodules, with an emphasis on the current algorithm considering the most recent American Thyroid Association of thyroid nodule and differential diagnosis guidelines 2021. Methods: Relevant literatures were reviewed, including serial PubMed, google scholar, and direct science searches supplemented with additional articles. The quality and strength of recommendations were adapted from the Clinical Guidelines Committee of the American College of Physicians, which in turn was developed by the Grading of Recommendations Assessment, Development and Evaluation workshop. Results: We update the diagnosis, initial evaluation, establishment of treatment goals, and approaches to locoregional disease control.

Keywords: *thyroid nodule, thyroid cancer, thyroid disease management, update therapy for thyroid lumps*

Introduction

In the last three years, several sets of guidelines for the treatment of thyroid nodules have been released. The American Thyroid Association published the first set. And the American Telecommunications Association (ATA) was the second. The Association of Clinical Endocrinologists (AACE) and the Association Medicine Endocrinologist (AME) have teamed together to form the Association of Clinical Endocrinologists (AACE). The American Thyroid Association (AME) and the European Thyroid Association (ETA) are two organizations dedicated to thyroid health. Although there are many similarities between these principles, each set takes a somewhat different approach to it. Advising on which nodules should be biopsied.

Thyroid nodules, whether single or numerous, are quite prevalent in clinical practice. They are detected in about 5% -7% of the adult population once they are examined **[**1**]**.Because current ultrasound (US) technologies may identify tiny nodules, the percentage of thyroid nodules in unselected people has been reported to be as high as 67%**[**1**]**.And continue to be identified at a high rate due to the widespread use of different imaging methods (computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), and so on) that identify thyroid nodules "accidentally"**[**1- 2**]**. Thyroid nodules are clinically significant because they might suggest thyroid malignancy, which occurs in 10% -15% of nodules. And might indicates the possibility of thyroid malfunction (autonomous adenoma and toxic multinodular goiter), compressive symptoms, and aesthetic concerns **[**3**]**. The primary concern of patients and clinicians is to detect suspected malignancies as quickly and cheaply as feasible. as well as reducing unwanted thyroid surgery **[**4**]**. This article highlighted the current thinking on the workup of a de novo thyroid nodule. We emphasize the most current edition 2021 of the American Thyroid Association's (ATA) treatment recommendations for thyroid nodules and differentiated thyroid carcinoma **[** 5**]**.

Thyroid Nodule Definition:

A thyroid nodule, as defined by the American Thyroid Association's task committee on the management of thyroid nodules and differentiated thyroid cancer, is a discrete lesion inside the thyroid gland that is radiologically distinctive from the surrounding parenchyma **[**5**]**. It can be single, multiple, cystic, or solid, and it can be functional or not; therefore, the precise morphological features, thyroid functional status, and pathological assessment must be determined **[**6**]**. Thyroid nodules can be divided into two types: non-neoplastic and neoplastic. Thyroid nodules that are neoplastic might be benign or malignant **[**5-6-7**]**. Table 1 contains a list of the thyroid nodule's differential diagnoses.

Table 1. Clinical and pathological classification of thyroid nodule

- **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**

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

Patient history:
- 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; AntiTg, antithyroglobulin antibody; CT, compute tomography; MRI, magnetic resonance imaging; PET, positron emission tomography).

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	

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

(**Abbreviations:** MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; 18FDGPET, 18F-fluorodeoxyglucose positron emission tomography; 99mTcMIBI, 99mTc-2-methoxy-isobutyli).

Diagnosis Approach of Thyroid Nodule

The most essential step in the diagnostic process is to check for evidence of malignancy in the findings acquired from the patient's history, physical examination, laboratory tests, and imaging methods. Table 2 **[**8**]**. There are four key modalities to consider after proper history: clinical examination, thyroid function testing, thyroid imaging, and the FNA **[**4,9,**]** which will be reviewed briefly.

Clinical Examination: Most thyroid nodules are asymptomatic and are detected by the patient or a physician during a neck examination. Table 3 shows the characteristics (signs and symptoms) of thyroid cancer that can be detected in a variety of contexts, including a regular physical examination or a nodule discovered accidentally during an imaging test. **[**5,9,10**]**.

Laboratory Investigations: following a history and physical examination, a decision will be taken on whether to continue additional workup. If such workup is to be done, the first step is to acquire a Thyroid

Stimulating Hormone (TSH) result **[**5**]**. A suppressed TSH concentration suggests the need for serum free thyroxine (fT4) and free triiodothyronine (fT3) **[**4,6,11**]** determinations, as well as thyroid scintigraphy (if available) to observe regions of high (hot nodules) and low (cold nodules) iodine absorption **[**5**]**. Because functioning nodules have a low risk of malignancy, no additional cytologic examination is required unless there are multiple thyroid nodules **[**6**]**. Diagnostic US should be done in instances of normal or high serum TSH. A normal TSH should be followed by a needle biopsy if required, and a high TSH should be followed by a workup for hypothyroidism (anti thyroid peroxidase antibodies should also be collected to confirm Hashimoto's thyroiditis) in addition to a needle biopsy if indicated **[**5,11**]**. Antithyroglobulin and calcitonin were also tested in the laboratory. The importance of thyroglobulin paired with anti-thyroglobulin antibody tittering as indicators for disease recurrence in the follow-up of thyroid cancer following complete thyroidectomy and radiation ablation treatment **[** 4,9-11**]**. However, Antithyroid antibody tests (anti-thyroid peroxidase and anti-thyroglobulin) is not required in the routine work-up of a thyroid nodule **[** 5**]**.

Calcitonin is another study that ought to be mentioned. Calcitonin is a tumor marker that is sensitive and specific for medullary thyroid cancer. It is utilized in the diagnosis, monitoring, and prognosis of the disease (MTC) **[**11**]**. The development of a nodule should highlight the likelihood of MTC in the context of a family history of medullary cancer or multiple endocrine neoplasia syndromes, allowing for early radical surgery. The ATA recommendations do not advocate routine serum calcitonin tittering **[** 5**]**.

Imaging Techniques: Neck palpation is quite inaccurate in determining thyroid nodule shape and size. **[**3,6,9,10**]** As a result, imaging methods are becoming more popular, even though no imaging approach can predict the future. To some degree, morphological delineation of the lesion, including thyroid cancer risk classification, is dependent on imaging modalities.

Ultrasound examination of thyroid gland (US): The US examination in thyroid nodules is the initial imaging study of choice for thyroid gland assessment and it is extremely accurate and sensitive **[** 5,12,13**]**. A US examination was able to detect thyroid incidentaloma, which a physical examination could not. US indications in Thyroid nodules are the following: a) all forms of thyroid nodules, b) thyroid nodules with a history of neck radiation, and c) thyroid nodules with a history of family thyroid cancer, multiple endocrine neoplasia (MEN) type 2, even if the gland seems normal on palpation. A solid nodule, hypoechogenic, microcalcifications, uneven contours, subcapsular location, invasive growth, multifocal lesion, increased nodule blood flow on Doppler (when TSH is normal), and suspicious regional lymphadenopathy on US are all signs of cancer. **[**14**]** A ratio of the nodule's anteroposterior to transverse diameter (AP/T) greater than one suggested malignancy **[** 11**]**. Cystic, isoechoic nodules with uniform borders, no calcification, and no invasive development are typically regarded benign **[**13**]**.

In the presence of worrisome US characteristics, the number of nodules and their size are not predictive of malignancy, since a nodule smaller than 1 cm is just as likely as a bigger nodule to house neoplastic

cells. According to the ATA 2021 guideline, nodules as tiny as 1 cm should be biopsied and should be monitored depending on risk factors (Table 4)**[**5**]**. Enormous nodules are also worthy of attention; some nodules are so large that it has been suggested that they should be surgically removed rather than undergoing a biopsy. In A Cross Sectional study on Predictors of Malignancy in Solitary Thyroid Nodule conducted by S Sujitha-2020, FNA findings were commonly false-negative in patients brought to surgery with nodules larger than 4 cm. Due to their size, they frequently impact speech and swallow function, and as a result, big nodules (4 cm or more) may be suggested for surgical surgery because FNA is less reliable in assessing them **[**15**]**.

Scintigraphy of the thyroid gland: Thyroid gland scintigraphy employs one of the radioisotopes of iodine (typically 123I) or technetium-99 pertechnetate (99Tc) **[** 3-6,9,10**]**. It is advised in individuals with suppressed TSH to utilize it before needle biopsy to determine if a nodule is functional or not **[** 16**]**. As a result, a nodule is classified as functional or "hot" (tracer uptake greater than the surrounding normal thyroid), isofunctioning or "warm" (tracer uptake equal to the surrounding thyroid), or nonfunctioning or "cold" (i.e., has uptake less than the surrounding thyroid tissue) **[**16**]**.

Contrary to popular belief, scintigraphy offers functional rather than morphological information. **[**17**]** Scintigraphy has mostly been supplanted by US, although it still serves at least two functions: detecting hyperfunctioning nodules when a low TSH is detected on first testing, and, to a lesser degree, deciding which nodule(s) to sample in patients with numerous nodules **[**6,16,17**]**. FNA is not required for hot nodules since they seldom contain malignancy **[** 6,16**]**. It is the cold nodule that, based on size and US features, necessitates FNA.

Fine needle aspiration: In order to make biopsy judgments, uncertain nodules should be considered as nonfunctioning and subjected to cytological examination. **[**5,16**]** Examining Cytology and Histology Aspiration with a fine needle is the most critical investigation, and it should never be skipped if a thyroid nodule is present. There are three primary factors to examine when classifying and deciding whether a nodule should be FNAed: the patient's history, the size of the nodule, and the US characteristics (Table 4, ATA guidelines for FNA threshold) **[**5**]**.

FNA may be done with or without US guidance in the setting of a palpable nodule **[**18**]**. It is recommended that US-FNA be performed in the following cases: 1) nonpalpable nodules larger than 1 cm, 2) palpable nodules smaller than 1.5 cm, 3) deeply found nodules, 4) nodules in close proximity 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 lymph It is appropriate to do interval thyroid US follow-up for nodules that do not meet the criteria for biopsy.

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.

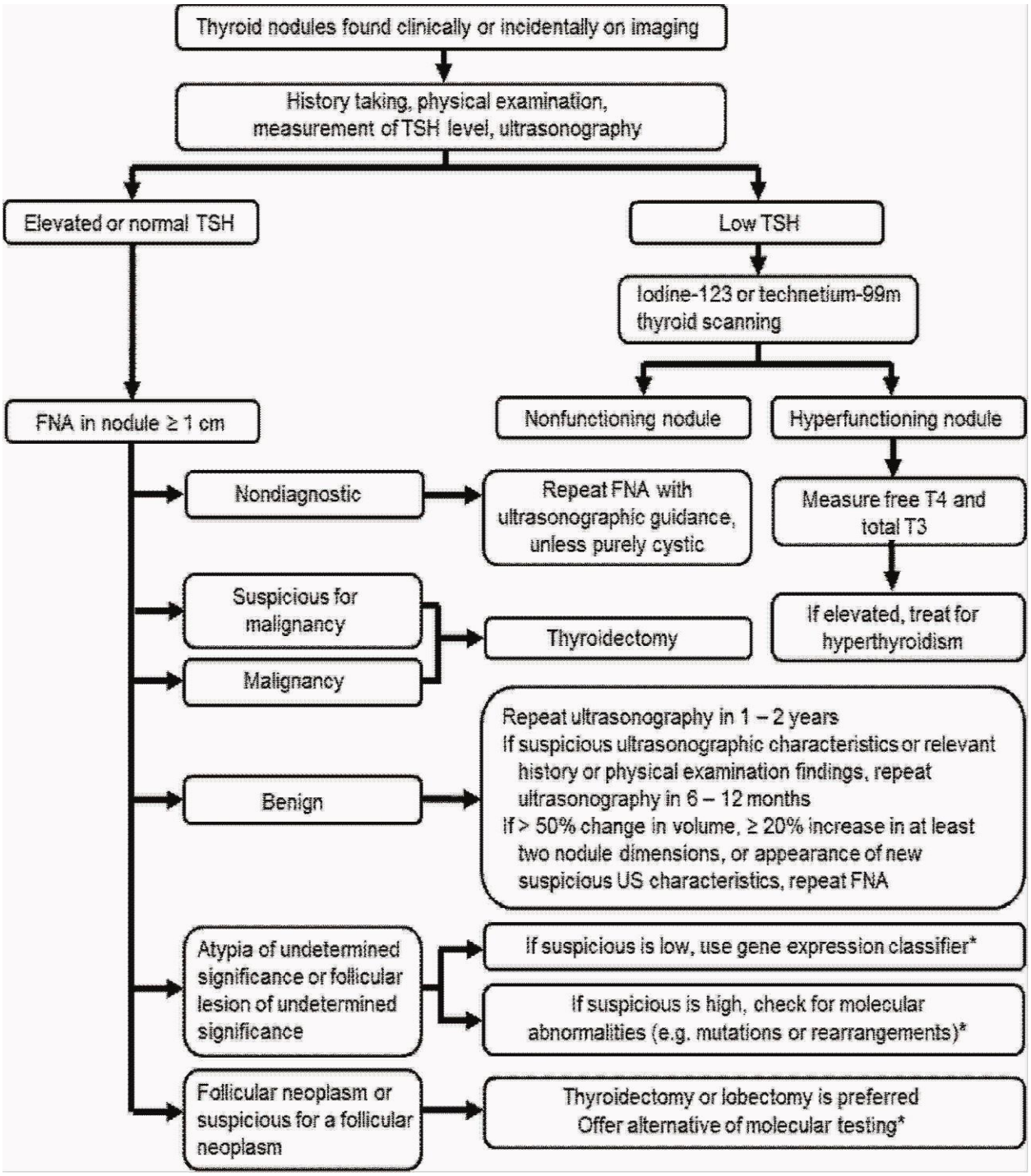

Figure 1. Algorithm for evaluation and treatment of thyroid nodules. Source: Burman KD and Wartofsky

L. N Engl J Med 2015. * Molecular abnormalities are not subjects of this article

Approach to Management:

The treatment of thyroid nodules is mostly dependent on the FNA results [5]. Benign, malignant, suspected malignancy, atypia of uncertain significance or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm or suspicious for a follicular neoplasm (FN/ SFN), and non-diagnostic are the potential reports [19]. Aside from the cytological diagnosis, the treatment approach may be influenced by the patient's age and gender, as well as the features of the nodule (size, consistency, activity, and number), as well as whether or not it is functional [4,5,9,10]. Figure1 and Table 5 depicts treatment methods.

Asymptomatic benign euthyroid nodules require just close monitoring and yearly or biannual US and TSH testing [5]. Nonetheless, benign thyroid nodules do require therapeutic intervention on occasion, particularly when they become big and produce obstructive symptoms [3,7,10,20]. Any form of malignancy, or the inability to rule out malignancy, suggested the necessity for surgical excision. The scope of the operation is determined by the type of tumor. If no additional risk factors exist, a simple hemithyroidectomy may be suggested as the first step in the therapy of follicular neoplasm or as the last treatment for a tiny, solitary papillary carcinoma [20]. All other thyroid cancers need complete thyroidectomy with local node excision. A total thyroidectomy should be performed if the histology of the follicular tumor reveals the presence of cancer [5,7,20].

Surgical Treatment of Thyroid Nodule:

Surgery is typically indicated when there are malignant or suspicious cytologic characteristics and/or symptoms caused by the nodule, especially in younger individuals and when there are big nodules [8]. The ideal operation is to remove the afflicted node unilaterally [5,7,20]. Complications include transient and permanent unilateral vocal cord paralysis (1% - 2% and 0.5% - 1.0%, respectively), as well as temporary and permanent hypocalcemia (1% - 2% and 0.5% - 1.0 %, respectively), hematoma and infection. (0.5% and 0.3%, respectively [7]. The risk of complications rises in direct proportion to the length of the surgery. Routine L-thyroxine therapy is not indicated in patients with normal thyroid function postoperatively since it does not appear to inhibit thyroid development in the long term, at least in iodine-sufficient locations. [20,21] Surgery is seldom utilized in hyperthyroid patients with toxic nodules, although it is a possibility. The therapy of choice for “hot” nodules is radioactive iodine [4,6].

- Benign cytology: Some benign lesions, whether solitary or combined with multinodular goiter, require surgical treatment if they are big (>4 cm in diameter), have signs and symptoms of compression, cause discomfort, or are cosmetically significant. 20 Recurrent cysts following therapeutic fluid aspirations may warrant surgery since these lesions can include malignant cells in up to 10% of patients. All of the other benign nodules are amenable to medical treatment **[**21**]**.

Patients with benign cytology and minimal risk factors may still require follow-up for another 12 – 24 months, given the 5% false negative FNA findings. If the nodule develops considerably, the US-FNA must be repeated. Significant nodule growth is defined as an increase in diameter of 20% or more with a minimum rise of 2 mm **[**5**]**. In a patient with high-risk characteristics, such as those listed in Table 3, benign cytology may need diagnostic lobectomy. Patients with a prominent nodule in a multinodular goiter who are experiencing compressive symptoms require complete thyroidectomy and postoperative L-thyroxine replacement treatment. The existence of a toxic adenoma or a toxic multinodular goiter is another reason for surgery in benign thyroid nodules. **[**9,10,20**]**. To avoid a thyroid crisis complication, surgery must be performed after restoring normal thyroid function through adequate preparation with antithyroid drugs in the case of thyrotoxicosis **[**4**]**.

- Malignant Cytology: In most patients with malignant cytology or suspected instances, complete thyroidectomy is the therapy of choice to achieve loco-regional control. This also allows a thyroid cancer patient to have post-operative radioiodine (I131) ablation to treat the microscopic illness. **[**8,20,22**]** In the absence of local invasion, the sole exception might be a papillary microcarcinoma of the thyroid (1 cm). In this case, the ATA recommends lobectomy **[**5**]**.

Although this article concentrates on the investigation and treatment of thyroid nodules, a comprehensive analysis of the treatment of all thyroid cancers is outside the scope of our discussion. The following is a general management guideline for differentiated thyroid carcinoma.

A. Papillary thyroid carcinoma (PTC): The most prevalent kind of thyroid cancer is papillary thyroid carcinoma (PTC), which accounts for 80–85 percent of all thyroid malignancies **[** 3,7-10**]**. It has a favorable prognosis, and tumors larger than 1 cm are best treated with a complete thyroidectomy **[** 5,8**]**. Completion thyroidectomy is appropriate in individuals who have had a previous diagnostic lobectomy and are found to have PTC bigger than 1 cm on final pathology. **[**23**]** To reduce the risk of lymph node metastases, thyroidectomy should typically be completed within 6 months after the first surgery **[**7,10**]**. Although routine central compartment dissection is debatable, it is believed

that up to 50% of patients had neck metastases at the time of diagnosis **[**24**]**. There are no prospective, randomized trials comparing preventive versus therapeutic central lymph node dissection at the moment. The ATA now recommends therapeutic central or lateral lymph node removal in PTC for clinically positive nodes. However, recommendations for preventive neck dissection are less clear.

Prophylactic neck dissection may be performed in individuals with T3 or T4 tumors, while dissection "may be fairly avoided" in patients with T1 or T2 cancer **[**5**]**. Currently, lifelong TSH suppression is advised, albeit the degree of suppression and its duration are under consideration **[**8,23,24**]**.

B. Follicular thyroid carcinoma (FTC): This type of thyroid cancer is identified histologically based on capsular/vascular invasion and accounts for 10% of thyroid cancer **[** 3,7-10**]**. Routine FNA cytology is typically unable of distinguishing these histologic characteristics from follicular neoplasm (their benign counterpart). Thus, to confirm follicular cancer, AUS/FLUS and FN/SFN require diagnostic lobectomy **[**9,19,20**]**. If histology confirms this, the patient will require a total thyroidectomy later on **[** 5,22**]** The function of the intra-operative frozen slice of the thyroid in these individuals is fraught with controversy.

In a study of 564 individuals with thyroid malignancies, 70% of the patients had their frozen sections analyzed. According to the findings of this study, an intra-operative frozen section on thyroid tumors adds relatively little to surgical treatment. **[** 25**]** In contrast to PTC, which spreads mostly through the lymphatic system, follicular cancer spreads hematogenously. As a result, unless there are positive neck nodes on US and FNA, regular central compartment clearing is not recommended.

Radioactive I131 ablation and lifelong TSH suppression treatment, as well as PTC-like follow-up, are necessary **[** 8,23**]**. Post-operative therapy with radioactive I131 is used for three main reasons. First, RAI ablates or destroys any residual normal thyroid tissue, allowing thyroglobulin to be more specific as a tumor marker in long-term monitoring. Second, RAI is used as an adjuvant treatment in intermediate-risk patients to eliminate the remaining concealed tiny foci of well-differentiated thyroid cancer, therefore lowering the chance of recurrence. Finally, RAI can be used to treat high-risk individuals who have a macroscopic residual disease (remnant ablation) or distant metastatic illness **[**22,23**]**.RAI is now recommended for use postoperatively in patients with T3, T4, or M1 diseases, according to the 2015 ATA guideline **[**5**]** .

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

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

Nonsurgical treatment of thyroid nodule:

• Medical Treatment with levothyroxine: Although it is becoming less prevalent, thyroid suppression with levothyroxine (L-thyroxine) is still often used in the treatment of solid thyroid nodules in euthyroid individuals **[**26**]**. The goal is to reduce existing nodules, which is considered a good indicator that the nodule is benign **[**3**]**. The success of medical therapy of benign nodule(s) with L-TSH suppressive dosages, on the other hand, is debatable **[**5**]**. Young, healthy individuals with tiny, solid nodules from iodine-deficient areas appear to benefit the most **[**21**]**. Approximately 20% of solitary solid nodules retreat as a consequence of L-thyroxine treatment, and discontinuation of medication results in fast recurrence.

Long-term treatment, on average, has no substantial nodule-reducing impact. Growth can be inhibited or delayed, and additional nodules can be avoided from forming. However, this requires serum TSH to be lowered to subnormal levels (TSH goal 0.1 – 0.45 mIU/mL), which may have negative consequences

[21]. This level of TSH suppression, known as mild or subclinical hyperthyroidism, is linked to an increased risk of atrial fibrillation, other cardiac side effects, and decreased bone density, which might lead to osteoporosis [26].

L-thyroxine treatment should be avoided in patients with large nodules or long-standing goiters, especially if the TSH value is less than 0.5 mIU/mL, postmenopausal women or those over the age of 60, patients with osteoporosis, cardiovascular disease, or systemic diseases [21,26] .In addition, L-thyroxine treatment has little impact in individuals with a cystic nodule or those who have naturally low blood TSH levels with or without increased thyroid hormone levels [21]. For these reasons, its utility is dubious; at best, it can be used in younger individuals with tiny nodules who require the least amount of therapy. Routine suppression of L-thyroxine is no longer indicated for cytologically benign nodules [5].

• Radioactive iodine: If the patient has hyperthyroidism (toxic nodule), antithyroid medications (propylthiouracil or methimazole) can restore thyroid function; nevertheless, disease recurrence is common when treatment is discontinued [4]. Except for a few individuals who have a big nodule, for whom surgery is necessary, radioactive iodine is the preferred therapy. This is also true for the clinically euthyroid patient with a functional ("hot") nodule, whose therapy may be influenced by nodule size, which may induce compression or aesthetic disruption [6]. Furthermore, radioactive iodine therapy is utilized to avoid hyperthyroidism, annual risk of approximately 4% [4].

Pretreatment with recombinant human TSH has the potential to simplify and enhance radioiodine treatment of nontoxic nodular goiters; nevertheless, additional research regarding this technique is required [27]. Following a single dosage of radioactive iodine, the cure rate (i.e., restoration of thyroid function and appearance on a thyroid isotope scintigraphy) is 70%, and the nodule decreases 30-60% [22]. There are few side effects, except for rare occurrences of radiation thyroiditis and progression to Graves' disease. After 5 years, the incidence of hypothyroidism is around 10% and is unrelated to radiation dosage [27]. The long-term risk of cancer is unclear; however, it is thought to be minimal. The nonfunctioning (cold) nodule, whether solid or cystic, is unaffected by radioactive iodine. In the future, the potential of stimulating with recombinant human TSH before radioactive iodine therapy may lead to enhanced iodine absorption and also an impact on the solid and cold nodule [22].

• Percutaneous Ethanol Injection for Thyroid Nodule Destruction (PEI): US-guided PEI into nodules (particularly symptomatic cystic nodules) has been presented as a viable, safe, well-tolerated, and cost-effective alternative treatment approach for benign thyroid nodule in situ ablation [21]. Ethanol (70-100%) induces localized small artery thrombosis and coagulative necrosis, which leads to fibrosis and irreversible tissue ablation. It has been utilized to treat both independently functional and nonfunctioning thyroid nodules, whether solid or cystic. Based on a 50%-90% nodule volume decrease in thyroid nodules bigger than 30 gram, nearly half of patients with single nodule, nonfunctioning

thyroid nodules are relieved of clinical symptoms. Additional injections are ineffective [28]. It is an alternative for people who do not want to have radioiodine therapy or surgery [5]. However, to get a total cure, it is frequently necessary to repeat therapy. And because of the common, if transitory, adverse effects (especially local pain), PEI should be confined to carefully chosen nodules that are easily palpable in patients who refuse I131 and surgery [5,21]. This treatment, although is often performed in Italian facilities, is not a routine option, should still be categorized as experimental, and needs specialized technical expertise that can only be gained at a facility acquainted with interventional ultrasonography [29].

• Photocoagulation via Interstitial Laser (IL): In patients who cannot (or will not) undergo surgery, ultrasound guided ILP has been utilized as a non-surgical option in the treatment of benign, solitary, solid (both "hot" and "cold" nodule) [30]. One 10-minute treatment resulted in a 40% reduction in nodules and a substantial improvement in pressure sensations. These findings are comparable to those achieved with ethanol treatment. The ability to regulate the distribution of energy using a laser (thermal destruction) as opposed to chemical destruction via injection of ethanol may favor laser treatment in the long run.

• Radiofrequency ablation (RFA): When surgery is not an option RFA is a less invasive therapy for some types of benign thyroid nodules [21].

RFA treatment has mostly been used to reduce pressure sensations, improve aesthetic outcomes, and resolve thyrotoxic status in "hot" nodules. The effectiveness of RFA for “cold” nodules has mostly been assessed in terms of nodule volume reduction, pressure complaints, and aesthetic symptoms [31]. A recent study comparing the effectiveness and safety of surgery versus RFA in benign thyroid nodules found that both are effective treatments. When compared to surgery, RAI reduces nodal volume considerably and provides better benefits in terms of fewer post-operative complications, maintenance of thyroid function, and fewer inpatient days [32].

Follow-Up: The clinical, US, and cytological features of benign euthyroid thyroid nodules are used to guide follow-up [5]. Thyroid nodules are typically re-evaluated every 12 to 24 months using clinical assessment (history and physical examination), US, and TSH.

Cytologically insufficient, inconclusive, or ambiguous nodules may require more careful monitoring and repeat biopsies within 1 to 2 months. 10 Significant growths identified by the US (defined as an increase of more than 20% or greater than 2 mm) does not always indicate cancer because benign lesions grow bigger as well, but a repeat FNA should be considered. If additional clinical or US signs of malignancy emerge, the same recommendation applies [5,9]. In patients with differentiated thyroid carcinoma who have had a complete thyroidectomy and radioactive iodine ablation, thyroglobulin level monitoring is utilized to test for cancer recurrence [5,7].

Thyroid function should also be checked regularly (typically once a year) in individuals who have had ablative treatment (surgery or I131) **[**23**]**. A serum TSH measurement is commonly used to assess this. If hypothyroidism is detected, L-thyroxine replacement medication should be initiated, which requires yearly monitoring. Thyroid ultrasound after surgery can be used to track the progress of the residual gland.

Conclusion:

Thyroid nodule diagnosis and treatment are largely determined by early examination, clinical criteria, and the use of TSH measurement, US, and FNA as first tests. They must be useful, efficient, and cost-effective. FNA biopsy in multinodular thyroid can be limited to the dominant nodule, with specific consideration given to high suspicious pattern nodules on imaging. If malignant or questionable cytology is found, surgery is necessary. Rapid development and rising pressure effects, as well as cosmetic reasons, are all reasons for surgery. With apparently benign thyroid nodules, simple monitoring and L-thyroxine suppression are appropriate treatment options. Thyroid nodule ablation (ethanol injection and laser photocoagulation) has been used to destroy benign solid nodules in situ. Radiofrequency ablation (RFA) therapy is presently regarded as an experimental treatment technique. In some cases, radioiodine treatment (RAI) may be used to treat the condition. In the case of indeterminate cytology, diagnostic surgery may be required to rule out cancer.

Declaration of bias: The author states that no conflict of interest exists that would jeopardize the objectivity of this scientific study.

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