Tatlıpınar and Kartal, Thyroid Disorders Ther 2015, 4:2
DOI: 10.4172/2167-7948.1000181

Journal of Thyroid Disorders & Therapy

Review Article Open Access

The Evaluation of Thyroid Nodules

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Abstract

Thyroid noduler disease is a common clinical problem. A wide variety of pathologic conditions, including neoplastic, hyperplastic, and inflammatory diseases can lead to nodular enlargement of the thyroid. The high prevalence of thyroid nodules requires evidence-based rational strategies for their differential diagnosis, risk satisfaction, treatment, and follow-up. The main point of the approach of the thyroid nodule is detection of the malignant nodules and deciding for the surgical treatment. Physical examination, laboratory investigation, thyroid imaging and cytology can be used to evaluate thyroid nodules. After detection of thyroid nodule by physical examination or ultrasonography, thyroid function tests and fine needle aspiration (FNA) biopsy should be implemented. Although FNA cytology is gold standard method to evaluate thyroid nodules, experience is needed. Hence, if the information gathered from history, physical examination, US and other test results (Thyroid function tests, SC, CT, etc.) were integrated withFNA cytology, decision for surgery may be more accurate.

Keywords: Thyroid nodule, Fine needle aspiration biopsy, Ultrasonography

Introduction

Thyroid noduler disease is a common clinical problem. A wide variety of pathologic conditions, including neoplastic, hyperplastic, and inflammatory diseases can lead to nodular enlargement of the thyroid. The detection rate of thyroid nodules has increased due to use of high resolution ultrasononography (US) during the last two decades [1]. This is in paralel to increased incidence of thyroid cancer worldwide since malignancy comprises approximately 5% of all thyroid nodules irrespective of the size [2,3]. While the overhelming majority of thyroid nodules are benign, the primary goal of thyroid nodule evaluation is to determine if a nodule is malignant or benign and thus may or may not need surgery. In addition the initial evaluation should focus on exclusion of malignancy [4].

Thyroid nodules present a challenge in their diagnosis, evaluation and management. In medicine, every decision to either stop a workup or pursue with further workup is based on a balance of perspectives and clinical judgment. In addition the perspectives must include not only the cost of missing a cancer but also the cost of aggresively managing a mass that is not cancer.

Epidemiology

Many of the thyroid nodules are discovered during physical examination or incidentally with other imaging tests, such as carotid US, cervical magnetic resonance imaging or computerized tomography.

A thyroid nodule is a discrete lesion within the thyroid that is palpably and/or sonographically distinct from the surrounding thyroid parenchyma. A solitary thyroid nodule exists within a thyroid gland of normal dimensions and morphology, whereas a dominant thyroid nodule exists within a diffuse or multinoduler goiter [4].

The nodule can represent a cyst, a malignant or benign tumor, thyroiditis, Graves' disease, or colloid nodular disease. A palpable thyroid nodule is usually >1 cm. Prevalence varies considerably worlwide, depending on regional iodine sufficiency. Iodine deficient areas: up to 50% of adults. Iodine sufficient areas: Approximately 5% of adults [5]. On the other hand, the reported prevalence depends on the modality used for diagnosis and the age group. Tunbridge et al. found thyroid nodules upon physical examination in 2% of subjects in their 20s and 5% in their 70s [6]. A prospective study showed that 46% of the nodules (>1 cm) detected by US did escape detection by clinical examination [4]. Autopsy and prospective US studies in North America demonstrated asymptomatic thyroid nodules in 50 and 67% respectively [7,8].

Studies on the epidemiology of thyroid nodule function are rare. The scintigraphic evaluation of 60% of the solitary nodules detected by US in a random cohort of probands aged 41-71 years living in an area with borderline iodine deficiency revealed cold nodules in 46%, isofunction nodules 44%, and hot nodules in 6% [9]. Most hot nodules are easily detected by a thyrotrophin (TSH) level.

The high prevalence of thyroid nodules requires evidence-based rational strategies for their differential diagnosis, risk satisfaction, treatment, and follow-up.

Historical Importance

To determine whether the nodule is malignant, historical information must be obtained. Family history is important, as there is an inheritable form of thyroid cancer-medullary thyroid cancer. This can occur as a single disorder in a family or as part of the multiple endocrine neoplasia syndrome, MEN (II).

Thyroid nodules are more common in women and increase in incidence with age. Male sex and youth (<15-20 years) should therefore raise greater suspicion. Old age (>70 years) is also a risk factor for malignancy.

Exposure to radiation increased risk of both benign and malignant thyroid lesions persists for at least 3 decades beyond time of exposure.

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Received March 31, 2015; **Accepted** April 24, 2015; **Published** April 29, 2015

Citation: Tatlıpınar A, Kartal İ (2015) The Evaluation of Thyroid Nodules. Thyroid Disorders Ther 4: 181. doi:10.4172/2167-7948.1000181

Rapid enlargement, pain or tenderness over the nodule, dysphasia, dysphonia, or hoarseness are important clinical evoluation criterias for suspicious nodules.

Fixture of nodule, movement with swallowing, regional lymhpadenopathy are also important to evaluatethyroid nodules.

Pyhsical Examination

Ability to detect a palpable thyroid nodule on physical examination depends on location within the gland, superficial versus deeply embedded, anatomy of patient's neck, including degree of adiposity and experience of examiner.

Although thyroid nodules have an estimated prevalence of about 4% by palpation, the accuracy of clinical diagnosis of thyroid malignancy is low [10]. Clinical indications of malignancy may be: The size of the nodule (more suspicious if greater than 4 cm to palpation), gradual increase of the nodule's size, hardness and firmness of a nodule, cervical lympadenopathy, distant metastases, hoarseness, dysphagia, obstruction, local pain, Horner's syndrome [11-13].

Laboratory Investigation

Many investigative tools are available for the physician. Laboratory tests should be ordered to assess thyroid function, including a serum thyroxin and thyroid stimulating hormone (TSH) test [14]. Serum TSH measurement should precede imaging studies and fine needle aspiration (FNA) biopsy.

Thyroid Stimulating Hormone (TSH)- antithyroid antibodies

The majority of patients with benign or malignant thyroid nodules are euthyroid. Despite this, serum TSH measurement is recommended in all patients presenting with nodule [4,13,15,16].

In the case of normal or high serum TSH, diagnostic thyroid US should be done [4]. Even if the TSH is high, FNA is recommended as the rate of malignancy in nodules within thyroid glands with Hashimoto's thyroiditis is similar to nodules within thyroid glands without Hashimoto's thyroiditis. If TSH is high, antithyroid antibodies (anti-TPO, anti-TG) should also be evaluated to confirm the diagnosis of Hashimoto's thyroiditis [17, 18].

In the case of low TSH, a radionuclide thyroid scintigraphy (SC) (^{99}Tc or ^{123}I) should be obtained to document whether the nodule is functioning or not. Functioning nodules rarely harbor malignancy.

Calcitonin

Medullary thyroid carcinoma (MTC) makes up only 5% of thyroid malignancies; however, recent reports have concluded that prevalence of MTC ranges from 0.4 to 1.4% in unselected patients with noduler thyroid disease. The routine calcitonin (CT) measurement to improve the preoperative diagnosis of MTC in nodular thyroid disease remains controversial [16,19].

Some authors reported that calcitonin evaluation detects MTC in cases where other procedures such as FNA cytology failed, thus allowing early radical surgery [20,21]. Others report that there is no absolute threshold value for basal CT to discriminate thyroid MTC nodules from other etiology [22]. Data from nonrandomized, prospective studies mostly from European countries report that routine CT measurement can detect early and unsuspected MTC[13]. Yet, there seems to be no consensus on this issue, and outside Europe, the enthusiasm for ordering CT has not been accepted as a routine due to cost effectiveness [23]. The calcitonin measurement is proposed by 5% of the members of the American Thyroid Association during the assessment of a solitary thyroid nodule compared to 43% of the members of The European Thyroid Association [24]. The American Association of Clinical Endocrinologists/Associazione Medici Endocrinogi (AACE/AME) guidelines do not endorse routine CT measurement recommending the test only if FNA is suspicious for MTC or family history is positive for RET.

Today, the audience responce seems to acknowledge this ongoing controversy in thyroid practice, with 49% using, whereas 43% not using, routine CT measurement. The overwhelming majority of them are likely practising in Europe.

Thyroid Imaging

Ultrasonography

US was first used to detect thyroid nodules in 1967 by Fujimoto [25]. It is more accurate than palpation in identifying solitary or dominant nodules within a multinodular goiter and it approaches the frequency of thyroid nodules found in autopsy studies [7,10,26].

As recognized in guideliness for managing thyroid nodules published by The American Thyroid Association and other authoritative bodies, thyroid US should be part of the initial workup in all patients with one or more thyroid nodules [4]. US shows thyroid lobes size and nodule size, echo structure (diffuse, uninodular or multinodular), echogenicity (iso-, hyper- or hypoechoic structures) and adjoining neck structures. It is a noninvasive, inexpensive and practical procedure that can be used in daily routine practice. Nowadays, the use of high tecnology US equipment may detect nodules as small as 2 to 3 mm, which raises the question of which thyroid nodules are clinically relevant for further evaluation [3].

Single thyroid US characteristics of thyroid nodules are of limited sensivity and specifity [27]. However, results are highly operator dependent and clearly superior in clinics or centers with good experience and expertise [27].

Several studies have investigated whether US can be used in the differentiation of benign and malignant thyroid nodules. For each thyroid nodule, gray-scale and color or power Doppler US are used to evaluate the size, location within the thyroid gland, composition, echogenicity, regularity of the border or margin around the nodule, presence of a halo, vascular pattern, as well as presence or absence of coarse or fine calcifications. Hypoechogenicity, microcalcifications, irregular or microlobulated margins, taler-than-wide shape, and increased intranodular vascularity were found to be independent risk factors for malignancy [4,28] (Table 1). İncrease in the size of nodule, especially when significant, may be a predictor for malignancy and an indication for repeating biopsy [29]. Although the relation of microcalcifications to malignancy seems to be controversial, the presence of intrinsic microcalcification seems the most statistically reliable criterion on which increased suspicion for malignancy in thyroid nodules [30-32]. The use of Doppler flow analysis may improve the cancer predictive value of a thyroid lesion. Intranodular blood flow can be detected in a greater percentage of malignant nodules [33,34]. Thyroid US should always include evaluation of the neck for abnormal lymph nodes. Lymph nodes with metastasis from thyroid malignancy tend to become rounded and bulging and lose their hilar echoes as their structure becomes disrupted [35].

Benign	Malign
Hyperechoic	Micro / İnterrupted rim calcifications
Halo sign or a smooth magrin	Irregular magrin
Significant decrease in size over time	Significant increase in size over time
Normal, small reactive, cervical nodes	Presence of abnormal cervical lympadenopathy
Pure cystic nodule	Hypoechogenity
Spongioform nodule	Absence of Halo or incomplete halo
Absent of peripheral vascularity	Height>Width
Uninterrupted eggshell calcifications	Increased intranodular flow

Table 1. Ultrasound characteristics of thyroid nodules.

Keeping in mind that none of the US features and tecniques alone is sufficient to differentiate benign from malignant tumors, it is reported that 66% of benign nodules have at least one positive US predictor of papillary thyroid cancer and 66% of papillary cancers have at least one nonsuspicious US feature. However, a combination of these sonographic features is more successful in pointing out a subset of nodules at high risk for malignancy [36,37].

Scintigraphy

SC provides functional rather than morphological information, contrary to US. Its use is recommended in patients with suppressed TSH to document whether a nodule is functioning or not [4,38].

Recent AACE/AME guidelines have suggested that a radioisotope thyroid scan should be ordered only if TSH is below the lower limit of normal range or if the patient has large single nodule or a multinoduler goiter, and is from an iodine deficient area.

Nodules with increased uptake (hot) are toxic adenomas and account for 5-10% of palpable nodules, but thyroid malignancy is only minority among them (1-4% chances only) [39,40]. On the other hand, nodules that accumulate radionuclide equal to surrounding tissue (warm), or nodules with low uptake (cold), are most often benign (80%) but may be malignant in to 25% and therefore require FNA biopsy (Figure 1). The role of SC in the routine evaluation of all patients with thyroid nodules is questionable according to some cost-effectiveness studies [41].

Computed tomography scan/magnetic resonance imaging

Computed Tomography Scanning and Magnetic Resonance Imaging role is limited,except to see the spread and compression of neighbouring structures.

Positron emission tomography (PET)

It is usually employed in patients with metastatic disease. It offers valuable information in localizing a primary tumor in patients with neck nodal metastases from an unknown primary malignancy and in the detection of recurrent disease. After thyroidectomy, FDG-PET has proven useful in patients with clinical or serological evidence of recurrent or metastatic thyroid carcinomas but negative whole body radioiodine SC [42].

Cytology

Fine needle aspiration biopsy

Any solitary or dominant thyroid nodule larger than 1 cm should be evaluated by FNA cytology, unless proven to be hyperfunctioning. Micronodules needs to be evaluated by cytology only in the event of suspicious finding at US (solid hypoechoic with microcalcifications) or personal history [13].

Since FNA is considered to be most accurate and cost-effective in the preoperative investigation of thyroid nodules, it is accepted as ''gold standard'' in the management of thyroid nodules (Figure 2) [13,43].

However, it is clearly an imperfect tecnique for many reasons. First, the results are non-diagnostic in approximately 15% to 20% of cases [44,45]. Second, there is a false negative rate of approximately 3% to 5% [46]. Third, there is wide variability in interpretative skill regarding cytopathology of the thyroid nodule. It is estimated that approximately 18% of all patients who have an FNA ultimately come to surgery for nodule excision based on positive, suspicious, or non-diagnostic results, and that most of these nodules are benign [44,47]. Of these patients who have surgery it is estimated that only 15% to 32% have cancer [44,47].

In medical centers with long-standing experience, diagnostic (adequate) biopsies obtained from solid nodules range from 90 to 97% [44,48,49]. It is more difficult to achieve a diagnostic biopsy from a cystic or mixed nodule [50].

If US guidance is used instead of palpation, the value of FNA diagnostic accuracy enhances [50-52]. US helps direct the needle tip to the desired site, avoiding vessels in close vicinity to the nodule or areas of central necrosis, which often yield nondiagnostic specimens [53]. AACE/AME guidelines suggest US-FNA for the following clinical settings: any size nodule with a history of radiation, or family history of RET; any size nodule with suspicious US features; for nodules with extra capsular growth or cervical nodes; an impalpable or small (< 1 cm) nodules [54].

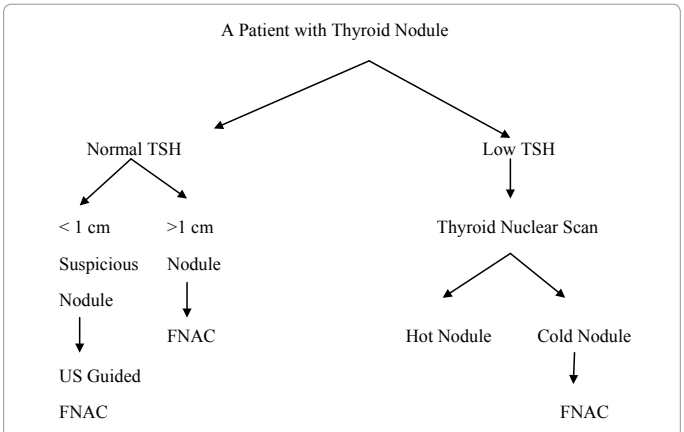

Figure 1: Evaluation of a patient with thyroid nodule (FNAC: Fine Needle Aspiration Cytology).

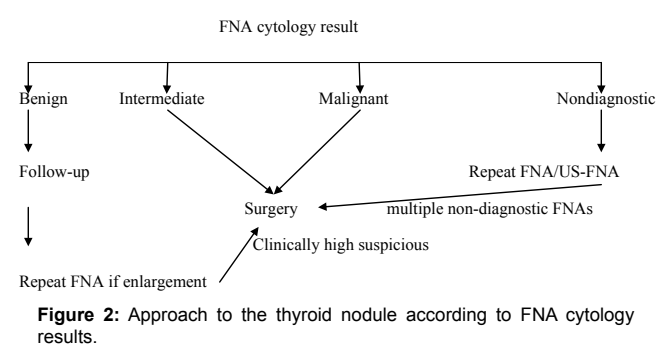

Figure 2: Approach to the thyroid nodule according to FNA cytology results.

The results of cytological examination of samples obtained by FNA biopsy can be categorized as benign or negative for malignancy (65%); positive or malignant (5%); nondiagnostic or unsatisfactory (20%); and suspicious or indeterminate (10%) [27]. Nondiagnostic or unsatisfactory smears are caused by inadequate cellularity and should be repeated. The repetition of FNA on initially nondiagnostic cases produced diagnostic results in more than half of the cases [54,55]. Noting that despite good tecnique approximately 5% of nodules remain nondiagnostic and should be surgically removed. Overlapping cytological features may cause indeterminate or suspicious results of FNA [16,56,57]. In particular follicular thyroid cancer and Hurthle cell carcinoma can not be distinguished cytologically from follicular and Hurthle cell adenomas, respectively, after FNA [43,58]. These nodules are classified as carcinomas if capsular or vascular invasion are found histologically after surgery.

AACE/AME guidelines suggest simple follow-up for cytologically benign thyroid nodules; repeat US was not recommended. AACE/AME suggests reaspiration only for enlarging nodules, recurrent cysts, or for nodules not shrinking after thyroxine (T4) therapy.

Lucas et al. rebiopsied 116 patients with benign FNA and found no missed malignancy, concluding that reaspiration is not necessary [59]. On the other hand, Chehade et al. followed 235 patients with benign FNA for an average of 2.9 years and repeat FNA found malignancy in 1 (0.4%), concluding that rebiopsy reduces false negative rates [60].

Management of nodule with indeterminate cytology still regenerates controversy. The cancer risk among these specimens ranges from 15 to 75%, approximately 15% for follicular neoplasm. Immunhistochemical markers have neither regularly nor reliably separated benign from malignant lesions [27]. AACE/AME guidelines consider surgical excision as the best management; repeat biopsy or large needle biopsy is not recommended.

Conclusion

Despite many strong similarities, a few relevant differences are present in clinical practise on thyroid nodule managements. This is probably due to the variable availability of the tecnical resources and professional skills and to the changing prevalence of thyroid disease in different regions of the world. The main point of the approach of the thyroid nodule is detection of the malignant nodules and deciding for the surgical treatment.

To establish a diagnosis of thyroid disease that caused the nodule, thyroid function tests and FNA biopsy should be implemented. If TSH is low, a radioisotope thyroid scan is essential for the detection of toxic nodule which has minor risk for malignancy. There is no consensus on routine CT measurement to improve the preoperative diagnosis of MTC. However, family history and FNA cytology is important to decide measurement of CT. Although FNA cytology is a very reliable and powerful screening method in the preoperative diagnoses of thyroid nodule, long standing experience is needed. Hence, if the information gathered from history, physical examination, US and other test results (Thyroid function tests, SC, CT, etc) were integrated withFNA cytology, decision for surgery may be more accurate.

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