In the name of God

Shiraz E-Medical Journal
Vol. 6, No. 1 & 2, January and April 2005

http://semj.sums.ac.ir/vol6/jan2005/thyroid.htm

New Insight into the diagnosis and management of thyroid nodule.

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این مقاله دارای امتیاز بازآموزی است. جهت کسب اطّلاعات بیشتر، لطفاً اینجا را کلیک کنید.

Solitary thyroid nodule

A solitary thyroid nodule is a palpable discrete swelling within an otherwise apparently normal thyroid gland. Nodules must approach 1cm in diameter to be consistently recognized on palpation, although according to the location of nodule within the gland and the anatomy of the neck, this size varies. With time, they may enlarge, shirnk or even disappear spontaneously, but most do not change appreciably[1,11]. Most are actually the only palpable nodule of multiple nodules in small clinically unrecognized multinodular goiters[2].

The majority of thyroid nodules are benign lesions. But about 5% of all palpable nodules are found to be malignant[3]. So the main objective of evaluating them is to exclude malignancy. How can the less common malignant one be distinguished from the much more common benign nodules? What treatment strategies may be used to avoid unnecessary testing while identifying the few patients who require therapy? These issues are central to the purpose of this review.

Prevalence of thyroid nodules: In large population studies, nodules have been reported in 3-7% of adults living in iodine sufficient areas with a 5: 1 female/male ratio. But, a discrepancy exists between the true prevalence of thyroid nodules and the number that apparent by physical examination. 50% of the thyroids examined during surgery[4], at autopsy[5] or by ultrasonography[6] harbor nodules, a frequency 10 times that found by palpation alone. Thyroid nodules are two to three fold more frequent in iodine-deficient areas[7]. The frequency of thyroid nodules, increases throughout life[8]; a 5 to 10% lifetime risk exists for developing a palpable thyroid nodule.

On the other hand, cancer is relatively uncommon among thyroid nodules(5%). Clinical thyroid cancer has a prevalence of approximately 2.5 cases per 1000 persons[9] and thyroid cancer-related deaths are

rare[10]. 1 out of 15 thyroid cancers manifests itself as clinical disease and the majority remains occult for life[7].

Differential diagnosis: The differential diagnosis of thyroid nodules includes mostly the disorders shown in Table. They should be differentiated from nonthyroidal lesions such as parathyroid cyst, thyroglossal cyst, lymphadenopathy, anneurysm, cystic hygroma, laryngocele or bronchocele which may appear in same area.

Figures vary according to the evaluating method of thyroid nodule. 42-77% and 15-40% of surgically removed nodules are colloid nodules and adenomas respectively[11], while 8-17% are carcinomas[11]. When evaluated by FNA cytology, 27-60% are colloid adenomas and 26-40% are simple follicular adenomas[12]. Mostly, colloid nodules are dominant nodules within glands that prove to be multinodular on surgery, sonography or thyroid scan. Many of them are cold nodules and incompletely encapsulated, but a few are hot nodule (hyperfunctioning)[11]. Follicular adenomas, tend to be single lesions with well-developed capsules. They are classified according to the size or presence of follicles and the degree of cellularity. Simple colloid (macrofollicular) adenomas are the most common form. Although macrofollicular type have no malignant potential, about 5% of microfollicular adenomas, 5% of hurthle-cell adenomas and 25% of embryonal type prove to be follicular cancers with careful study[11,13]. Thyroid carcinomas usually present as a solitary palpable thyroid nodule. The most common type of malignant nodule is papillary carcinoma followed by follicular, medullary and anaplastic types of thyroid carcinoma.

Table1. Differential diagnosis of thyroid nodules

Benign lesions
Follicular adenoma
Colloid (macrofollicular)
Simple (Normofollicular)
Microfollicular (fetal)
Trabecular (embryonal)
Hurtle cell (oncocytic)
Teratoma
Lipoma
Dermoid cyst
Malignant lesions
Follicular cell
Well-differentiated carcinomas
Papillary
Follicular
Anaplastic (Undifferentiated) carcinomas
Medullary thyroid cancer
Metastatic carcinomas
Sarcoma
Lymphomas
Other thyroid abnormalities
Thyroiditis
Hemiagenesis
Thyroid cyst
Infection
Granulomatous disease (e.g., sarcoidosis)

Diagnostic approach to the thyroid nodule:

History and physical examination:

Statistical probability of thyroid cancer can be estimated from a comprehensive history and physical examination. The history is useful mostly for identifying the presence of factors favoring malignancy, because when nothing in the history favors a malignant nodule, a small but disturbing number of patients still have thyroid cancer. The physical exam may be more valuable but in general, signs and symptoms are not sufficiently sensitive or specific to allow selection of candidates for surgery.

Although the presence of following clues in history and physical exam do not exclude the possibility of thyroid cancer, they are in favor of benign disease:

· Symptoms or signs of hyperthyroidism or hypothyroidism

· Family history of benign thyroid nodule or goiter
· Soft, smooth, mobile nodule

Some authors also has included in this list the family history of hashimoto's thyroiditis or autoimmune thyroid disease[14]. But the diagnosis of thyroid lymphoma should be considered in patients with a previous diagnosis of hashimoto's thyroiditis, especially in women older than 50 years of age[15].

The following clinical findings increase the suspicion of malignant thyroid disease:

· history of radiation to head and neck whether in low doses or high doses is the single most important risk factor for cancer although it also increases the incidence of nonmalignant nodule[16].
· Extremes of age (<20 and >70 years old)
· Nodules in male are more likely to be malignant (two fold risk compared to female)
· Nodules accompanied by dysphagia, hoarsness, rapid growth, obstructive symptoms
· Firm, fixed, hard and irregular nodules, although a hard nodule may be caused by chronic thyroiditis or calcified adenoma, whereas a soft nodule may be a cystic papillary cancer.
· Cervical lymphadenopathy
· Horner syndrome
· A family history of multiple endocrine neoplasia type 2A or 2B.
· A family history of pheochromocytoma, hypercalcemia, mucosal abnormalities or medullary thyroid cancer should raise the suspicion of the medullary thyroid cancer.

Previous history of thyroid cancer or polyposis (Gardner syndrome)

Some believe that the incidence of malignancy is greater in solitary nodule than in a prominent nodule in the context of MNG[17]. However, similar frequencies of cancer have been reported among those who have solitary or multiple nodules on palpation[4,7].

In both retrospective and prospective studies, the sensitivity and specificity of history and physical examination for detecting thyroid cancers were about 60% and 80% respectively. In these series, only about 20% of patients with later confirmed malignancy had negative history and neck exam when initially seen. So, findings in the history and physical exam should not be ignored and can be used in directing the use of the available diagnostic studies.

Laboratory evaluation:

TSH should be measured in all patients with thyroid nodule. Abnormal thyroid function does not exclude the possibility of malignancy, but it decrease the suspicion in most cases.

Thyroglobulin may be elevated, as in all other goitorous conditions, and therefore is not a valuable tool in differential diagnosis. Its value lies in serial determination after cancer being diagnosed and most or all of the thyroid gland has been removed for treating malignant nodule.

Often in hashimoto's thyroiditis, the size and consistency of gland resemble a solitary nodule or bilateral nodules. In this situation the presence of antithyroid peroxidase (Anti-TPO) and antithyroglobulin antibodies are helpful for diagnosis. But, evidence for hashimoto's disease, dose not eliminate the possibility of cancer.

Several reports recommend routine measurement of calcitonin in patients with nodule[18,19]. However medullary thyroid cancer constitutes a small percent of thyroid malignancies and an even smaller proportion of thyroid nodules. On the other hand, the high frequency of false positive results may prompt a thyroidectomy despite a reassuring cytologic results. So in patients with a family history of medullary carcinoma, calcitonin level (basal or stimulated) and specific genetic testing should be determined. In the absence of such history, most clinics has not adopted calcitonin determination as a cost-effective or necessary measure in all patients with thyroid nodule.

Thyroid scan:

It provides a measure of the iodine-trapping function of nodule compared with the surrounding tissue. So, a thyroid scan dose not identify the presence of a nodule, but

rather assesses the regional uptake or function. Based on the pattern of uptake, 85% of nodules are classified as "cold" (decreased uptake), 10% as "warm" (similar uptake compared to the surrounding tissue) and <5% as hot (increased uptake with suppression of uptake in surrounding tissue). "Hot" nodules are exceedingly unlikely to be malignant. "Warm" and "cold" nodules can be malignant in 5-8% of cases. Thus, thyroid scan has low diagnostic specificity despite their high sensitivity for nodules >1cm in diameter. The limitation of thyroid scan is that only about 10% of nodules are delineated as benign and results are uncertain in the remaining 90%. In addition, nodules smaller than 1cm in size are below the discriminating power of most of the available scanning devices[20].

Different isotopes are available for thyroid scan. ^{123}I scanning is recommended because it avoids the problems with technetium and also the radiation burden of ^{131}I. The problem with technetium scan, although it is quick and convenient, is that results may be misleading in a small number of patients. A few technetium identified "warm" or "hot" nodules may be hypofunctional on iodine scan and a few of these nodules with discordant technetium and iodine scans are malignant[14].

The major role of scan is in confirming the functional status of a suspected autonomous nodule (ie those with suppressed TSH). Also it is particularly useful in evaluating asymmetric nodular goiter, hypertrophied lobes simulating nodules or masses and substernal masses.

Thyroid scans are particularly useful in patients with indeterminate cytologic results, because in such patients hyperfunctioning nodules are almost always benign[11]. Patients with cytologically benign findings upon FNA, would not benefit from subsequent scan unless thyroid hormone suppression therapy is being considered, then a nuclear scan will identify functioning nodules, for which levothyroxine therapy could lead to thyrotoxicosis.

Neck radiography, MRI and computed tomography (CT):

Neck x-ray has been used to identify calcification pattern of malignancy, but it has limited usefulness. Shell-like calcifications are most typical of benign cyst. Patchy or "signet ring" calcification occurs in old cysts and degenerating adenomas[20]. Fine, stippled calcifications (Psammoma bodies) have high specificity for papillary carcinoma. Flocculent deposits are more characteristics of medullary carcinoma[15].

MRI and CT scan are not superior to ultrasonography except in cases of substantial goiter and have no role in the assessment of nearly all patients with thyroid nodule.

Thyroid sonography:

Ultrasonography can not be used to determine the nature of a lesion as benign or malignant in most situations. Simple cystic nodules are seldom malignant and such a finding is reassuring[20,21]. However, purely cystic nodules are extremely rare[21] and cystic lesions >4cm in diameter may pose a significant cancer risk[22]. Therefore sonography is not routinely recommended in the initial evaluation of a thyroid nodule unless it will be needed to guide FNA biopsy.

Sonography remains an important tool for follow-up of both benign and malignant thyroid lesions. It provides an objective and sensitive indicator of whether a nodule is enlarging or decreasing in size over time, once the decision is made not to operate. An enlarging nodule would at least warrant a repeat FNA biopsy. Also it is very helpful in long-term follow-up of patients with thyroid cancer by detecting small or otherwise inaccessible nodule and lymph nodes that could represent recurrence of cancer[14].

Positive predictive criteria of malignancy in sonography include solid hypoechoic nodules, presence of calcifications, irregular shape, absence of halo and absence of cystic elements[23]. However, as stated before nodules that can be clearly

identified as benign by sonography are uncommon.

Fine needle aspiration biopsy:

FNA biopsy is safe, inexpensive and reliable. Its use leads to a better selection of patients for surgery than any other tests. So it has become the initial test for evaluating thyroid nodule and the most effective method available for distinguishing between benign and malignant nodules. It has decreased the number of unnecessary surgery by more than 50% and doubling the incidence of finding malignancy in resected specimens[13].

American association of clinical endocrinologist (AACE) recommends FNA biopsy of all thyroid nodules when the possibility of malignancy is appreciable and when the patient is a candiate for surgical and nonsurgical cancer treatment[14]. AACE also recommends FNA biopsy even when suspicion of cancer is very high because foreknowledge of the cancer cell type aids in the planning of surgical procedure[14]. Other indications for FNA include a dominant localized abnormality in thyroid gland in those with Grave's disease or Hashimoto's thyroiditis[24] and a rapidly growing diffuse thyroid enlargement[24]. In the latter group anaplastic carcinoma or lymphoma should be ruled out.

Experience and good technique are important for obtaining an adequate sample which should be reviewed by an experienced cytopathologists. Higher proportion of unnecessary surgery or using more expensive other diagnostic methods may result when an unskilled physician performs the biopsy or an inexperienced cytopathologist interpret the specimen. Conventionally, appropriate criteria for adequacy of specimen include at least 6-8 cell clusters smeared on slides or from cytospin cell preparations or RBC lysing solution preparations[14]. Recently, the papanicolaou society of cytopathyology has published guidelines that do not specify a certain minimal number of follicular cells, but instead stress the importance of assessing the amount of colloid in determining specimen adequacy[25].

Traditionally, suction technique is used for FNA. The needle is placed into the nodules several times and cells are aspirated into a syringe. The gauge of needle varies from 22-29 depending on the vascularity or fibrous consistency of the nodule. Care should be taken to avoid excessive blood dilution, crush artifact or air-drying of wet-fixed material. Recently, nonsuction technique has been introduced and recommended by some authors as a better method[24]. It is simple, produce specimens that are less bloody and is particulary effective for aspirating small lesions[24]. However, the conventional suction technique sometimes yields more material than the nonsuciton technique and vice versa, so it is unwise to use one technique to the exclusion of the other[24].

If an adequate specimen is obtained, three cytologic results are possible: benign, malignant and suspicious or indeterminate. Approximately 70% of samples show benign pattern. 4-5% of specimens are positive for malignancy and about 20% of specimens are suspicious or inadequate[26]. The suspicious or inadequate group are approximately equally divided. Inadequate or non diagnostic specimen contain too few cells for accurate interpretation. Sometimes, the cytologic report of an acellular or hypocellular sample is "no malignant cells seen", such report is a false conclusion of a benign FNA specimen and should be avoided[14]. A repeat FNA should be performed in nondiagnostic samples which may yield sufficient material for diagnosis in about half the cases. But even repeated attempts may fail. Many persistently nondiagnostic specimen may be malignant with a reported incidence between 37%[27] and 50%[28]. In such situation, either close observation or surgical removal is the best option. Some recommend a trial of TSH suppression in nondiagnostic specimen to see the response of nodule[29]. However, the diagnostic value of TSH suppression is doubtful, because some carcinomas do shrink while a

significant percent of benign nodules do not shrink. Whether sono-guided FNA can reduce the incidence of inadequate specimen is unclear with contradictory opinions[30,31].

Benign result can be followed safely. The mean sensitivity of FNA is 83% (range: 68-98%). The rate of false negative results ranges from 1-6%[21,23] and is chiefly due to sampling errors or misdiagnosis[32]. Sampling error tends to occur with very small (1cm<) or very large (>4cm) nodules, hemorrhagic nodules or MNG[32].

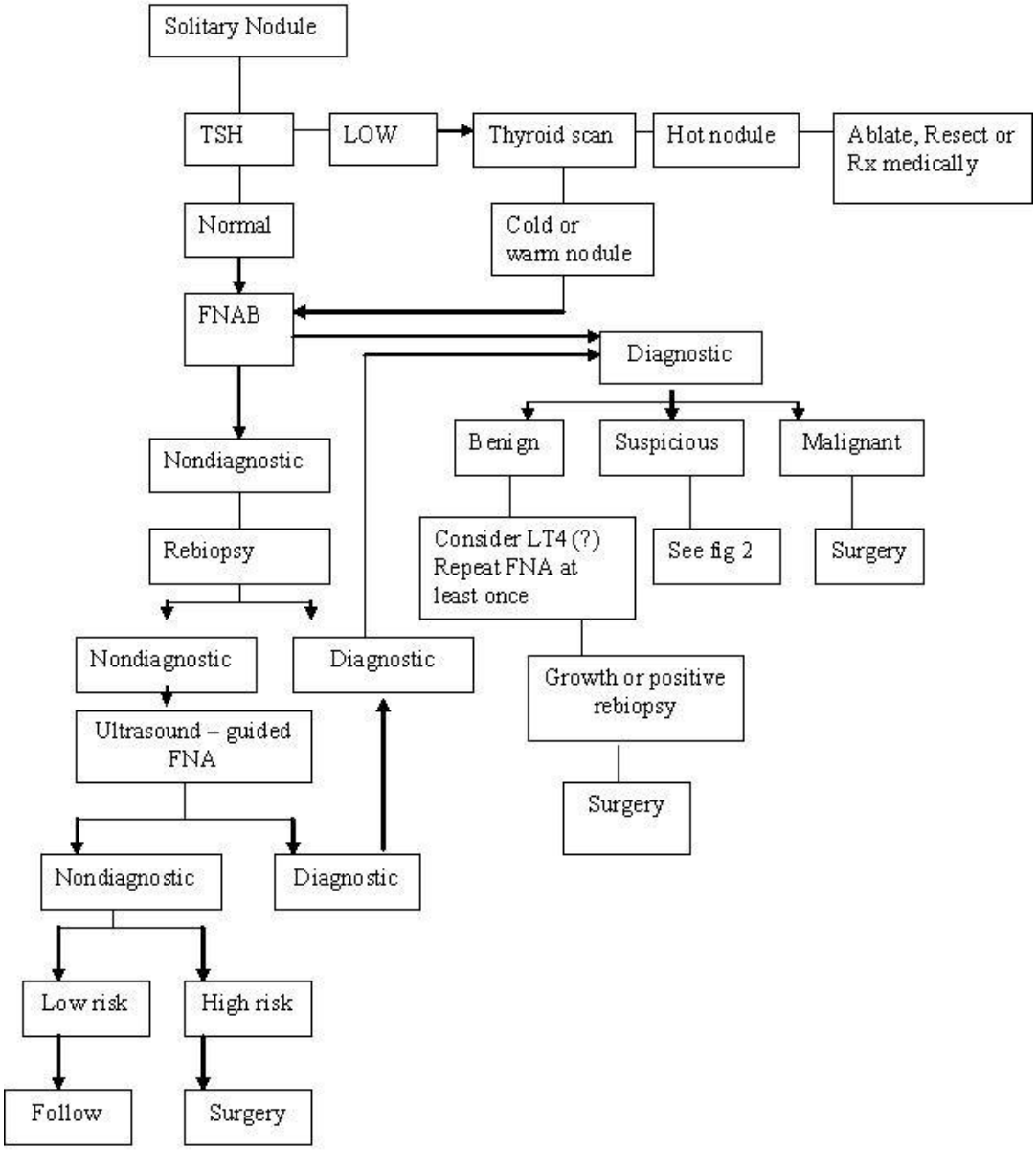
The diagnosis of papillary thyroid carcinoma (PTC) by FNA is particularly reliable with sensitivity and specificity approaching 100%. Medullary thyroid carcinoma, primary thyroid lymphoma and anaplastic carcinoma can also be detected by FNA according to their characteristic cytology, but the anaplastic carcinoma may sometimes be indistinguishable from metastatic tumor to thyroid[33]. The main limitation of FNA is the differentiation of benign from malignant follicular neoplasms. Evidence of capsular invasion, essential for proving malignancy, requires surgical excision. The sensitivity and specificity of FNA for detecting follicular carcinoma is less than for PTC. If strict criteria for malignancy are used, sensitivity may be as low as 8%. If any follicular neoplasm that is not clearly benign is classified as cancerous, sensitivity rises to >90%. But this leads to decreased specificity to 50%[23]. So, this seriously limits usefulness of FNA in iodine deficient area, where the incidence of FTC approaches PTC and where the prevalence of both follicular adenomas and hyperplastic adenomatous nodules are high. To circumvent these problems, immuno histochemistry method has been used that shows promise in improving the accuracy of FNA for follicular lesions[34]. There is controversy about the role of large needle biopsy for clarifying the nature of follicular lesions[11,35]. Some author report a high degree of accuracy for detecting follicular carcinomas with intraoperative frozen section, however, its contribution to management of solitary thyroid nodules remain controversial[11,36].

Another important limitation of FNA, which can lead to diagnostic confusion, is that from 10-20% of all cytologic specimens are suspicious or ideterminate. This category include: suspicious for papillary carcinoma, hurtle cell neoplasm and cellular follicular lesions or follicular neoplasm[14]. Of these, about 20% are from malignant nodules[11]. However, no effective method has been found to identify malignant lesions that yield indeterminate cytologic result upon FNA, except for some promise about using immunohistochemistry methods[34] for follicular neoplasm as discussed before.

Management of thyroid nodules:

An algorithm for evaluating the single thyroid nodule has been shown in Fig.1

Fig 1. Algorithm for evaluation of single thyroid nodule.



Benign thyroid nodules:

As the incidence of false-negative FNA result is low, most patients with benign findings can be followed without surgical treatment. They should be followed at periodic intervals with careful history and physical examination, and if needed appropriate thyroid function tests, ultrasonography or reaspiration should be done.

In fact, many advocate repeating FNA within 2-5 years to confirm the benign nature of nodule. Rebiopsy should also be performed at any time that the nodule enlarges or otherwise becomes suspicious.

Patients with history of irradiation present a special situation. Historically, due to their high cancer rate, they have been immediately referred for surgery in spite of benign FNA. Some now advocate to deal with this group as with other benign nodules[37], although sufficient evidence for the reliability of benign results is still lacking.

A long lasting controversy is the role of levothyroxine suppression therapy for patients with benign thyroid nodules to reduce the size of the nodule or to prevent its further growth[37-40]. Spontaneous regression of nodules in about 50% of patients makes the interpretation of suppressive trial results difficult unless careful controlled studies is done. The lack of universal efficacy makes such therapy optional in most patients. A recent meta-analysis[39] supports the observations that keeping TSH low with levothyroxine may prevent enlargement in some patients and unsuppressed benign nodules may grow. A recent large randomized controlled trial[41] showed reduced nodule size.

Overall, about 30% of nodules may decrease in size with levothyroxine, although the success rate varied from 0 to 68 percent in different studies[37,42-43]. When the patient and physician decide to select levothyroxine therapy, it seems prudent to give thyroxine in doses sufficient to suppress TSH to 0.2-0.4 mU/ml for 6-12 months[11]. If a nodule dose not decrease in size after 6-12 months of suppressive therapy, treatment should be discontinued as little benefit is likely to result from long-term treatment. After 6-12 months, in those who responded the levoathyroxine dose should be decreased to maintain TSH in the low normal range[11]. The physician and patient must weight the benefits of long-term therapy and the potential risks. Decreased bone density and cardiac arrhythmias such as atrial fibrillation may develop especially in elderly and postmenopausal women.

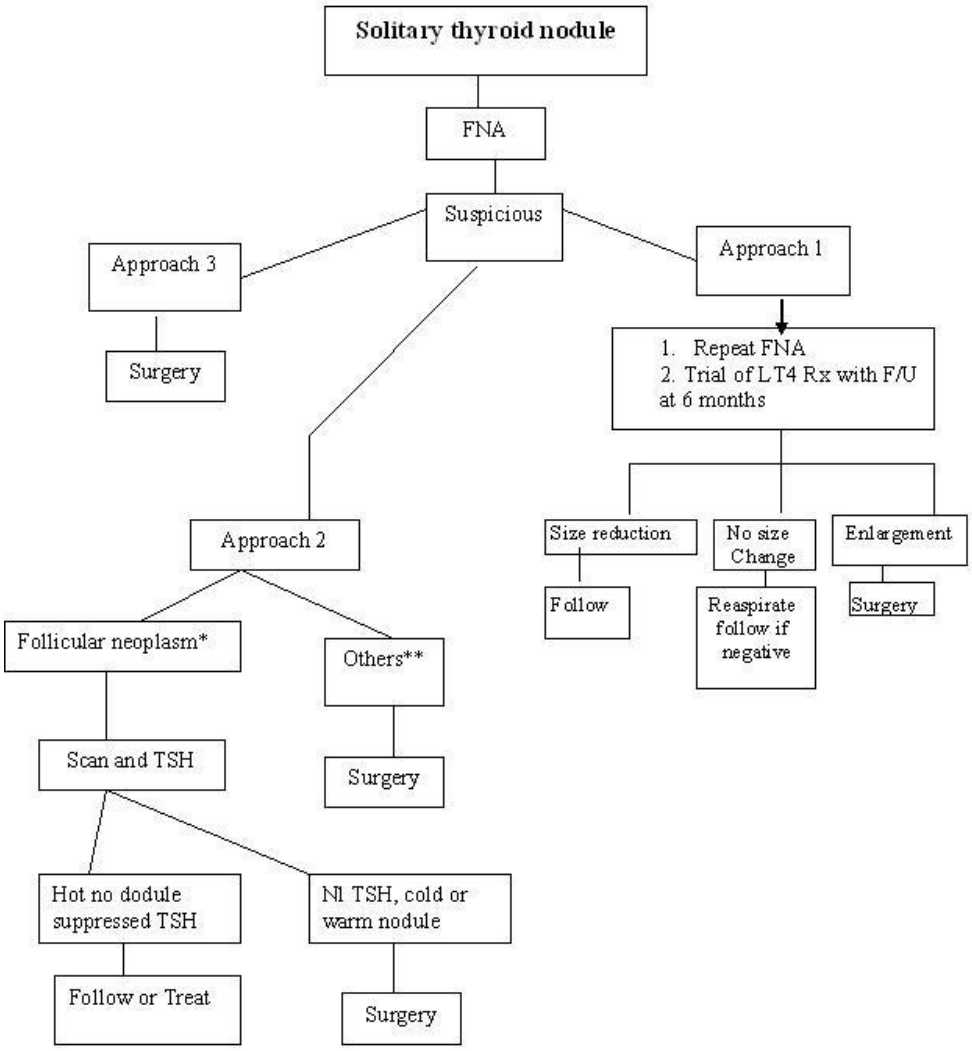
The same controversy exist about the role of levothyroxine suppression therapy in euthyroid patients after a thyroid lobectomy for a benign nodule. However, patients who benefit most from suppression therapy postoperatively are those who received radiation in childhood[16]. Levothyroxine reduced the recurrence rate of thyroid nodules in this group to almost five times lower than those who did not received therapy postoperatively[16].

One of the most challenging clinical questions is what to do about a thyroid nodule that grow after it is has been identified as benign by FNA. The coherent management of this situation will vary depending on biology of nodule in concern. Some are TSH regulated so levothyroxine therapy may prevent or reverse enlargement. Others are controlled by poorly understood mechanisms that must be elucidated before effective medical treatment can be designed, a few are autonomous requiring ablation and a few are missed malignancies that should be exiced.

Suspicious thyroid nodules:

Three different approaches have been proposed for managing this group of thyroid nodules[11,14,15,44] which is shown in Fig2. Anyway, thyroid nodules with suspicious FNA results should be surgically removed if shown not to be autonomous in function (i.e., cold nodules). But some proceed to surgery without performing thyroid scan if initial TFT is normal[44].

Fig 2. Three different approaches for managing suspicious thyroid nodule



* Sheets of follicular cells seen.
** Small groups of uniform follicular cells with little colloid

Autonomously functioning thyroid nodules:

As stated before, these nodules are almost never malignant. All patients with thyrotoxicosis need treatment. Also many patients with subclinical thyrotoxicosis especially older patients and those in postmenopausal period should be treated because of risk of osteoporosis and cardiac implications of subclinical hyperthyroidism. Therefore, treatment of asymptomatic patients with functioning nodules is decided on an individual basis.

Radioiodine ablation is the treatment of choice for most patients. Hypothyroidism occurs in <10% of patients over the next 5 years. For patients older than 20 years with nodules <3cm, radioablation is an appropriate treatment if the risk of eventual hypothyroidism is acceptable. Patients with nodules >3cm accompanied by pressure symptoms are most readily treated with surgical excision. Surgical excision is also often used in young patients (<20 year). Ethanol injection has been used successfully in some centers[45]. Repeated injection will lead to size reduction and normal thyroid function in most patients.

Hyperfunctioning nodules may undergo hemorrhagic necrosis. It will lead to loss of function and pain. The previously hyperfunctioning nodule may then appear

as a cold nodule on scan which together with the history of pain could be misinterpreted to represent a carcinoma.

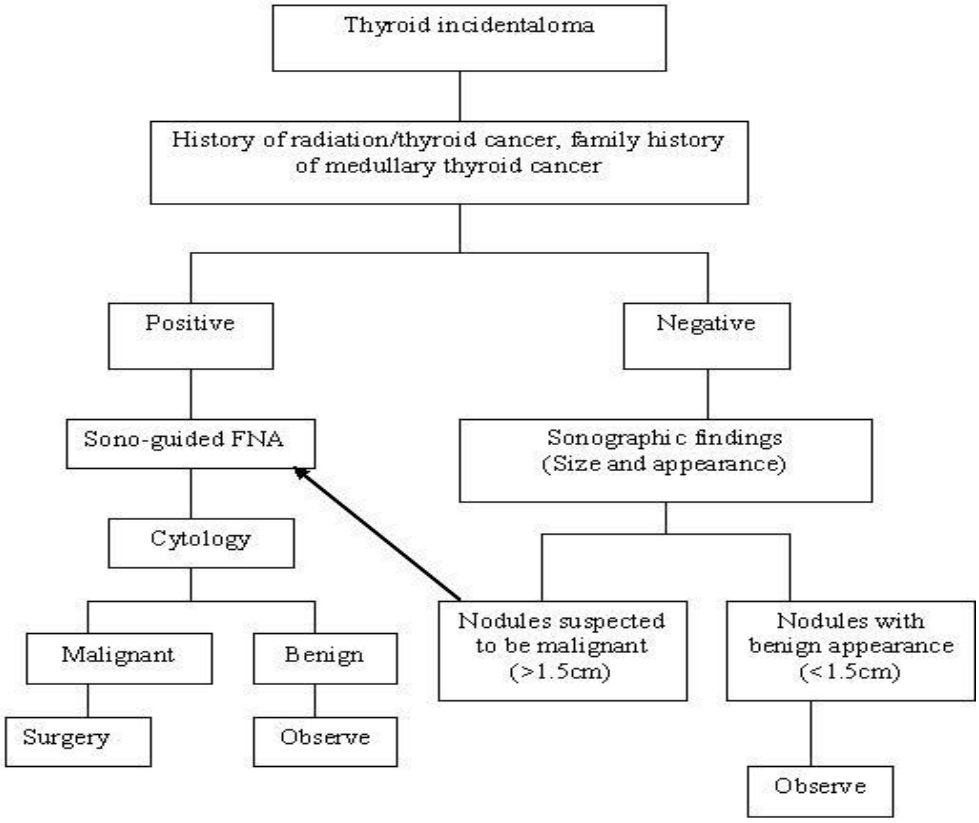
Malignant thyroid nodules:
The treatment of almost all malignant nodules is surgery. Exceptions include some patients with anaplastic thyroid cancer or lymphoma. In cases of well differentiated thyroid carcinomas radioablation with high dose iodine after surgery should be given. Life long thyroxine therapy after surgery is of great importance as it results in fewer tumor recurrence[11].

Cystic thyroid nodules:
Their risk of malignancy is[14] slightly lower than solid nodules (2-4%). About one-third of palpable nodules shows various amounts of cystic changes. Many are mixed cystic/solid lesions. It is the nature of solid component that is of primary clinical importance. Almost half such nodules disappear permanently after one or more aspirations[11]. Those that recur, even after repeated aspiration, are usually large (>4cm) and their aspiration are often bloody but with insufficient material for diagnosis; these should be considered for surgical removal[11]. No convincing evidence exists that thyroid hormone therapy reduces the risk of recurrence[11,15]. Sclerotherapy with ethanol or tetracycline has been used with variable success, but is often painful and may be complicated by leaking of sclerosing agent into surrounding tissue[46].

Thyroid nodules in children:
True solitary nodules occur in 0.2-1.3% of pediatric population. The presence of malignancy in such nodules is much more likely than in an adult. The frequency of malignancy is estimated to be 15-25%[14,47]. Malignancy rates decrease to 11% in adolescence[47]. The same diagnostic and therapeutic approach which is used for adults can be used for children[37,48].

Thyroid Incidentalomas:
Nonpalpable thyroid nodules found on imaging studies of neck (thyroid incidentalomas) are usually smaller than 1.5cm and present a management dilemma for clinicians[49,50]. The risk of malignancy is low for these nodules (<5%)[49]. Treatment strategy that has been proposed[49,50] is to observe those nodules which are <1.5 cm when the patient lacks risk factors for malignancy including history of radiation to head and neck, family history for thyroid cancer or history of previously treated thyroid cancer. Some sonographic features that mandate further investigation even in nodules less than 1.5cm in those who are low risk for malignancy include: Hypoechoic lesions, incomplete peripheral halo, an irregular margin and presence of internal microcalcifications[49]. The next appropriate step in those who need further evaluation is sono-guided FNA. Treatment should then be determined on the basis of cytologic finding. In others follow up every 6 months to 1 year with neck palpation is sufficient. If nodules become palpable FNA should be done. During follow-up, sonography or thyroid scans rarely indicated[49-50]. An algorithm has been proposed by Tan and Gharib which is shown in Fig 3[49].

Fig 3. Approach to thyroid incidentaloma



Conclusion

Thyroid nodules are common and usually benign. The main objective of evaluating thyroid nodules is to exclude malignancy. Diagnostic evaluation begins with comprehensive history and physical examination. Most patients with thyroid nodules have normal thyroid function tests. Nonetheless a TSH level should be obtained first. If the TSH is suppressed, a thyroid scan is the next step to determine if the identified nodule is "hot", as these types of nodules are almost never malignant and FNA is unnecessary. In the euthyroid patients, FNA should be the next step. Despite problems with nondiagnostic or suspicious results such a strategy has proved to be efficient and cost effective. The FNA is particularly reliable for detecting PTC. The differentiation between benign and malignant follicular lesions is often not possible using cytology alone. Despite the clinical advantages that are provided by FNA, the clinician should not dismiss the importance of other clinical prognostic indicators to optimize timely treatment. The main indications for surgery are malignant or suspicious cytologic findings although different approaches have been recommended for suspicious nodules (Fig2). Benign nodules are treated with levothyroxine or be followed without suppression, although most authorities do not recommend the routine use of LT4 therapy because it may be associated with adverse effects.

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