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Review Article

The Thyroid Nodule: New Diagnostic and Therapeutic Approaches

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Abstract

The thyroid nodule is a neoformation that occurs within the thyroid gland in about 1/3 of the population, usually with normal thyroid function. Females are more affected than males (4:1 ratio) in areas with sufficient iodine intake and increases in areas with mild or severe iodine deficiency. The most affected age ranges between 30 and 50 years old, but using the high-resolution ultrasound study its frequency reaches 20-68% of the population and age also decreases, affecting young people. Using a high-resolution ultrasound, the structure of the thyroid nodules can be solid (therefore made up of cells), mixed (partly liquid and partly solid), or completely liquid (cyst). The thyroid nodule can appear in a normal-sized gland or in a goiter; it can be single or multiple, unilateral or bilateral. Elastography exam can be added to improve the diagnosis.The causes of the appearance of a nodule can be familiar, related to the origin area (iodine deficiency), after external been radiations exposure (during pediatric or young age), or ionizing radiation or radioactive fallout, after a trauma in the neck region (hemorrhagic cyst), or from unknown causes. The most frequent diagnostic method for the detection of thyroid nodule is the high-resolution ultrasound with color doppler, which can be performed both for a specific reason, but also randomly for other organs evaluation (breast or neck vessels control). The nature of the thyroid nodule occurs with the fine needle aspiration (FNA) biopsy by ultrasound guide, with the subsequent cytological examination. The pathologist expresses the diagnostic opinion according to an international classification (Bethesda Classification System). For a more in-depth diagnosis, the new molecular biology methods can also be used searching for possible onco-gene modifications. The percentage of benign nodules is prevalent (90%) compared to thyroid carcinomas. Thyroid nodule therapy can only be follow-up or using thyroid hormone suppressive therapy (L-Thyroxine) or surgery. New therapies for nodules reduction, such as laser photocoagulation therapy, the use of radiofrequency and the high intensity focused ultrasound, have recently been introduced. Typically, these techniques are reserved for those patients with absolute or partially contraindications to surgery. The data published in the literature are encouraging, however other studies will be necessary to evaluate their concrete reliability and success in particular in large size nodules.

Keywords: *Thyroid Nodule; Fine Needle Aspiration; Follicular Neoplasia; Bethesda Classification System; HIFU; RFA; L-Thyroxine Therapy*

Introduction

The thyroid nodule occurs inside the thyroid gland asymptomatically in about 1/3 of the population [1]. In fact, the thyroid function appears normal in the majority of patients, only in 10% of cases of hyperthyroidism (toxic adenoma or toxic nodular goiter) or hypothyroidism (Hashimoto's thyroiditis nodular variant) conditions can be highlighted. Females are more interested than males (4: 1) [2] and the most interested age has a range between 30 and 50 years old [3]. However, using high resolution ultrasound, the detection of nodules determines an increase in the percentage up to 68% in the population and the age of detection is also drastically reduced [4,5]. The recommended blood tests, when one or more thyroid nodules are detected, are the measurement of circulating free thyroxine (FT4), thyrotropin stimulating hormone (TSH), antithyroid antibodies (TgAb and TPOAb) and calcitonin. Most nodules are highlighted by high-resolution ultrasound with color-doppler of the neck region, which can be performed either because the patient has noticed an anatomical modification of the neck anterior region or for auto-palpation or for compression symptoms, or for other reasons (ultrasound of the breast, or evaluating the neck vessels, etc).

The prevalence dimension of the thyroid nodules is small (micronodule if the diameter is less than 10 mm), while others can reach dimensions of several centimeters. They can be appear in a single lobe of the gland or in both (bilateral) and can occur either in a normal gland volume or in a goiter. The structure of the nodule in the high-resolution ultrasound study can be solid, liquid or mixed (Figure 1). Again with the high-resolution ultrasound with color-doppler, suspicious elements such as hypoechogenicity, an absent halo sign, the presence of spray microcalcifications and an intra-nodular vascularization [6] can be identified (Figure 2). The elastography study is a recent technique that permit to evaluate the nodule consistence and then indicate the evidence of suspicious or not [7]. The integration of both techniques in the clinical work-up of thyroid nodules can thus significantly improve the accuracy of the diagnosis of thyroid nodules.

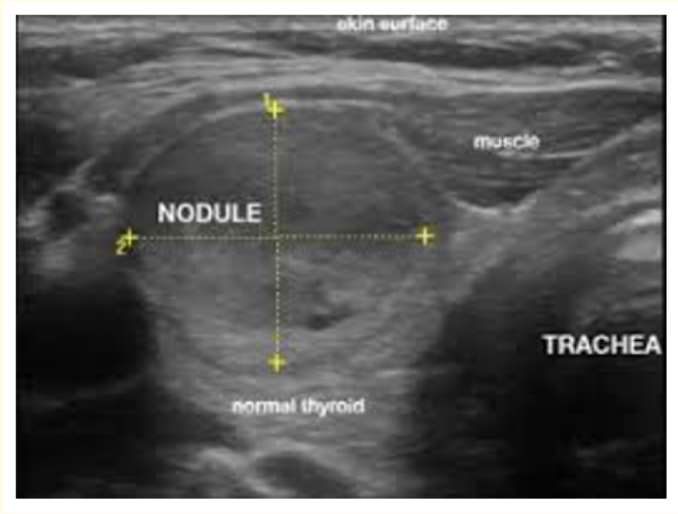

Figure 1: *Solid nodule in the right lobe of the thyroid without evidence of malignancy (right) and cystic nodule (left).*

Figure 2: *Hypoechoic nodule with microcalcifications (at the top); mixed nodule with increase of intra-nodular vascularity(suspicious) (below).*

In relation to the size and ultrasound structure, the latest published guidelines [2] indicate the opportunity to perform the fine needle thyroid aspiration (FNA) using a 22G needle under high-resolution ultrasound guidance and then cytology evaluation. The method is simple, painless, without particular complications and does not require local anesthesia but the informed consensus is mandatory. In thyroid micronodules (less than 10 mm) it's suggested to perform FNA only in case of high-resolution ultrasound suspicion evidence. The material extracted from the nodule with a normal syringe is laid out on slides, streaked and left to air dry. The cytological response occurs according to an international classification (Bethesda Classification System) [8].

Tir1	Non-diagnostic	10 - 25%
Tir1C	Cystic	5 - 10%
Tir2	Benign lesion	90%
Tir3A	Low risk follicular neoplasm	10 - 15%
Tir3B	High risk follicular neoplasm	5 - 10%
Tir4	Suspiciuos for cancer	1.2%
Tir5	Cancer	1-2%

Table 1: *Bethesda classification system.*

The non-diagnostic reports shouldn't exceed 10 - 20% of FNA. They are classified as inadequate and/or non representative (Tir1) [9]. The sample is inadequate when an insufficient number of cells for definitive diagnosis is collected from the nodule or only blood, or colloid or macrophages. Cystic nodules may be not aspirated for cytological examination, in fact, the possibility that a cysto-adenocarcinoma can be found, is very low [2]. The majority of nodules are cytologically classified as benign nodule (Tir2) (60 - 75%) [10]. A sample with at least 6 groups of 10 - 20 well-preserved epithelial cells from the nodule, can be considered representative. It included colloid goiter, autoimmune thyroiditis and granulomatous thyroiditis (de Quervain). In about 20 - 25% of the nodules we can have an FNA cytology indicative of indeterminate follicular proliferation or Tir3, as follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), a category that also encompasses the diagnosis of Hürthle cell neoplasm. This category, Tir3, has been divided into A and B; Tir3A classification, indicates indeterminate follicular neoplasm with low risk, (without nuclear and/or cytoplasmatic alterations) where only 10 - 15% of the nodules, histologically examined, can be a thyroid cancer. The Tir3B classification, represents a particularly subtle cytological entity with high risk (presenting nuclear and/or cytoplasmatic modifications), where about 25 - 30% of the nodules histologically examined, can be a thyroid cancer. Even with the help of molecular biology on this type of classification (Tir3A and B), such as the research for the oncogene mutation (BRAF, RAS, RET/PTC, Pax8/ PPR), doesn't allow with certainty to distinguishing a benign lesion from a malignant [11]. In cases where the cytological result is indicative of an indeterminate follicular neoplasm, the thyroid scintigraphy with 99mTc allows to exclude an "hot" or "warm" nodule from a non-functioning or "cold" nodule and therefore, allows to help the choice of therapy. Only a low percentage (1 - 2%) is represented by a classification Tir4 or Tir5 [2].

Therapy

In relation to the cytological classification, in patients with normal thyroid function with normal serum TSH and with normal circulating calcitonin value, independently if autoantibodies are present or not, the endocrinologist can establish the therapy schedule.

If the nodule is a Tir1 we can repeat the FNA at the next check and in the meantime check the nodule ultrasound. If over time the cytology doesn't allow a diagnosis and the nodule changes in size or structure, the advice is surgical removal. In patients with cystic nodule (Tir1C), in relation with volume, we can decide if treat it or not. If the cystic nodule is more than 2 cm we can use the percutaneous ethanol injection (PEI) or recently others [12-14]. In the majority (60-80%) the volume reduction can be observed at least after 6 months. In case of a nodule with Tir2 cytological classification, the therapeutic choice can be or only follow-up without adopting any therapy, or suppres-

sive therapy with L-thyroxine (LT4). There're publications in the literature, both for or against the use of LT4 suppressive therapy [15-17]. The suggestion is to use it in young patients without cardiological problems: in patients over 50 years old or with cardiac pathologies we suggest only to follow step by step and to keep in touch, to evaluate the progress of the nodule without therapy. In case of Tir3A cytology the council is to perform a close clinical follow-up (6 - 12 months) with the eventually FNA recontroled and if confirmed always, decide between follow-up or LT4 suppressive therapy. However, in case of ultrasound increase of the nodule, surgical removal is recommended. Surgery is always recommended in patients with Tir3B cytology independently to the molecular biology modifications, aware that the risk of thyroid carcinoma is 25 - 30%. In patients with Tir4 or Tir5 classification, surgical intervention is strongly recommended.

In patients with presence of antithyroid auto-antibodies (autoimmune thyroiditis nodular variant), with one or more thyroid nodules the percentage of malignancy seems to be greater than in patients without signs of autoimmune disease [18].

Alternative therapies

In the last few years, in patients with large size thyroid nodules with benign cytology (Tir2), non-surgical methods have been used to obtain the reduction of the nodules, especially if there are partially or absolute contraindications LT4 therapy or for surgery.

The use of interstitial laser-photocoagulation (ILP) ablation of thyroid nodules has been performed recently and seem to be an interesting results. Is a safe technique able to reduce about 50% the volume of benign thyroid nodules in the majority of treated patients. However, due to the great variability of results, an active follow-up is required [19]. Radiofrequency ablation (RFA) under high-resolution ultrasound is a percutaneous treatment that results in thermal tissue necrosis and fibrosis. As a result of this process, the nodules shrink. Clinical trials demonstrated a 50 - 80% durable nodule shrinkage after thyroid nodule RFA [20].

High-intensity focused ultrasound (HIFU) is a recent promising thermal ablation technique for treating benign thyroid nodules [21]. In fact its effectiveness in larger-sized nodules has been less well described. Single-session HIFU ablation was highly effective in causing shrinkage of benign thyroid nodules at six months, but the extent of shrinkage for larger-sized nodules (> 30 mL) was noticeably less than that of smaller-sized nodules. Both pre-ablation nodule volume and total energy per nodule volume were significant determinants of ablation success. For larger-sized nodules, additional HIFU treatment three to six months after initial treatment might be preferred over sequential treatment within the same session. However the need to use an operating room and a local anesthesia, without forgetting any complications such as local pain and possible risks both on the recurrent nerve and on the vagous nerve (eyelid ptosis) recommend its use only in patients with absolute contraindications to the surgical intervention.

Discussion

The thyroid nodule is a fairly frequent manifestation in the population (30%) with particular reference to females, both in young and adult age with prevalence for adults. The frequency increases in the general population by performing a high-resolution ultrasound. In most cases the thyroid nodule is asymptomatic, therefore it manifests itself with a normal thyroid function, and rarely associated with a condition of hyperthyroidism (toxic adenoma or multinodular toxic goiter) or hypothyroidism (Hashimoto's thyroiditis nodular variant). The majority of the nodules have small size (micronodules if less than 10 mm) or less than 2 cm and they make no signs of their presence, while in a low percentage of patients can be evidenced for anatomical neck modification, auto-palpation or compressive signs. The nodule may present as single or multiple in the normal thyroid volume or in a goiter, both unilateral or bilateral. The majority of the thyroid nodules are benign (90%) and only 1 - 2% are thyroid cancers. The high-resolution ultrasound with color doppler of the nodule can indicate whether there are reasons for suspicion as hypoechogenicity or halo sign absence, or spray microcalcifications or evidence of intravascular blood circulation at color doppler. The diagnosis can improve using elastography, when possible, evaluating the consistence of the thyroid nodule. Therefore, proceed with the fine needle aspiration of the nodule and with the cytological diagnosis. As we know the majority of the cases a benign lesion (Tir2) was diagnosed and therefore the endocrinologist can decide whether to start a medical

therapy with L-thyroxine suppressive therapy or to follow the patient only with ultrasound checks. The use of L-thyroxine suppressive therapy, when possible, permit to reduce the serum TSH stimulation on thyroid cells and then to control the growth and possible cells modification. Recently in patients with partially or absolute contraindications to surgery, the endocrinologist can try to reduce the nodule with interstitial laser-photocoagulation (ILP) ablation or with radiofrequency ablation (RFA) under high-resolution ultrasound. High-intensity focused ultrasound (HIFU) is a recent promising thermal ablation technique for treating benign thyroid nodules: however other studies will be necessary to evaluate their concrete reliability and success in particular in large size nodules. In patients with Tir3A cytology, the guidelines suggest a close clinical and high-resolution ultrasound checkup and with the eventually repetition of the FNA. The suggestion of surgery is recommended in case of nodule growth, during a follow-up or during L-thyroxine suppressive therapy, or ultrasound appearance of signs of suspicion at high-resolution ultrasonography with color doppler. In cases with Tir3B, Tir4 or Tir5 cytology results, surgical intervention is strongly recommended, as lobectomy or total thyroidectomy, in relation to the clinical experience and surgical collaboration.

Conclusion

In conclusion the thyroid nodule is a frequent manifestation in the population with particular reference to females, both in young and adult age. In most cases the thyroid nodule is asymptomatic, therefore it manifests itself with a normal thyroid function, and rarely associated with a condition of hyperthyroidism or hypothyroidism. The majority of the nodules have small size, while in a low percentage of patients can be evidenced for anatomical neck modification, auto-palpation or compressive signs. The nodule may present as single or multiple in the normal thyroid volume or in a goiter. The majority of the thyroid nodules are benign. The better method for the diagnosis is the high-resolution ultrasound can be improve using elastography. For the cytological diagnosis we proceed with fine needle aspiration of the nodule. In case of benign lesion (Tir2) the endocrinologist can decide whether to start a medical therapy with L-thyroxine suppressive therapy or to follow the patient only with ultrasound checks. Recently in patients with partially or absolute contraindications to surgery, the endocrinologist can use interstitial laser-photocoagulation or radiofrequency ablation. High-intensity focused ultrasound is a recent promising thermal ablation technique for treating benign thyroid nodules. In patients with Tir3A cytology, the guidelines suggest a close clinical and high-resolution ultrasound checkup and with the eventually FNA control. In cases with cytology results Tir3B, Tir4 or Tir5, surgical intervention is strongly recommended, as lobectomy or total thyroidectomy. Randomly perspective studies will be performed in a large population to understand the effectiveness ed efficacies of better therapy.

Declaration of Interest

The authors declare there is not conflicting of interest that could be perceived as prejudicing of this article.

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