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REVIEW ARTICLE

The current assessment and management of thyroid nodules

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ABSTRACT

Introduction. The widespread use of diagnostic imaging favored the increasing incidence of thyroid nodules. Although most of nodules are benign, their clinical importance lies in the need to exclude malignancy. In assessing and managing thyroid nodules may occur the phenomenon of overdiagnosis and overtreatment on one hand and the risk of missing an aggressive thyroid cancer on the other hand. The equilibrium that has to be reached by health care providers.

Materials and methods. We conducted a PubMed, MEDLINE, ISI Web of Science, Cochrane databases search for the relevant and recent guidelines, meta-analysis, randomized controlled trial, reviews articles related to „thyroid nodules assessment", „thyroid nodules management", „thyroid nodules guidelines", „thyroid nodules surgery".

Results. The initial assessment of thyroid nodules includes an evaluation of clinical, laboratory and sonographic risk factors. Due to the sonographic features and size, the nodules are selected for biopsy. Cytologically benign nodules are usually followed-up, minimally invasive techniques may be required in certain cases. In suspected or confirmed malignancy, the treatment options of thyroid nodules include surgery or active surveillance. The main controversies appear in management of nodules with inconclusive cytology, low-risk cancers, multinodular goiters, hyperfunctioning nodules, and thyroid incidentalomas.

Conclusions. Thyroid nodules due to the high incidence and heterogeneity of background diseases cannot be evaluated and managed in one standardized approach. In the existing literature, there are discussed multiple options for diagnosis and treatment of thyroid nodules. We have reviewed the guidelines recommendations, novel published data, and controversial questions for health care professionals, to understand and provide efficient, personalized, and cost-effective management of patients with thyroid nodules in order to avoid automatic intensive testing and intervention and balancing each case from the patient expectations and demands.

Keywords: thyroid nodules, cancer, assessment, management, surgery.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Discussion and decision-making on the most appropriate management of the patients with thyroid nodules.

The research hypothesis

Thyroid nodules are very common medical findings in adults and represent a multidisciplinary matter in which specialists have not reached a unique algorithm and consensus of diagnosis and treatment.

The novelty added by the manuscript to the already published scientific literature

This article reviews the main available evidence in order to offer guidance in health care of patients with thyroid nodules and points up particular considerations in thyroid nodules assessment and management.

Introduction

Thyroid nodules, solitary or in multinodular goiter are prevalent findings in the adult general population, which means that every second, a person has at least one nodule [1]. According to American Thyroid Association (2015), a thyroid nodule is a radiologically distinct lesion from the surrounding thyroid parenchyma [2].

The clinical significance of thyroid nodules relates to interference with thyroid gland function, causing compressive symptoms because of mass effect, and harboring a thyroid cancer.

Despite the fact that cancer occurs in 7-15% of cases, differentiation of benign from malignant nodules is a major issue in managing thyroid nodules. There is the possibility of overdiagnosis and overtreatment of thyroid nodules or the opposite, of missing an important clinical thyroid malignancy [1-6].

Materials and methods

A literature search was performed to identify meta-analysis, randomized controlled trial and reviews articles related to „thyroid nodules assessment", „thyroid nodules management", „thyroid nodules guidelines", „thyroid nodules surgery" in the PubMed, MEDLINE, ISI Web of Science, Cochrane databases. There were selected the most relevant and recent articles. The key guidelines eloquent on the issue were considered: The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [2]; AACE/ACE/AME Task Force on Thyroid Nodules, American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update [4]; ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee [5] and the American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults [6].

Results and discussions

Epidemiology and etiopathogenesis. The last 30 years has registered a substantial rise in the incidence of thyroid nodules. This phenomenon is due to the use of neck imaging studies. The prevalence rate in the detection of thyroid nodule by ultrasound imaging is 76%, by computed tomography (CT) or magnetic resonance (MR) imaging is 16%, by carotid duplex ultrasound is 9.4%, and around 2-3% by 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) [7].

Other reasons, which contribute, to a high incidence of thyroid nodules and thyroid cancer are residency in iodine deficiency regions, obesity, cigarette smoking, exposure to ionizing radiation. These factors lead to low levels of thyroid hormones into the bloodstream and in response TSH is released and stimulates proliferation of follicular cells with enlargement of thyroid gland and formation of thyroid nodules [3, 8, 9].

Moreover, the thyroid nodules are 4 times more frequent in females compared to males and this gender disparity is associated with pregnancy and influence of human chorionic gonadotropin on follicular cells as a homolog of TSH [10]. The incidence of thyroid nodules is increasing linearly with age and declines after reaching the plateau in the sixth-seventh decade of life [11].

Most nodules are derived from thyroid follicular cells. Based on etiology, thyroid nodules can be divided into non-neoplastic and neoplastic. Non-neoplastic nodules might be colloid nodules, nodules within Hashimoto's thyroiditis or Graves' disease, simple or hemorrhagic cysts. Benign neoplastic nodules are represented by follicular or oncocytic (Hürthle cell) adenoma, while malignant nodules can be papillary carcinoma, follicular carcinoma, Hürthle cell (oncocytic) carcinoma, anaplastic carcinoma, medullary carcinoma, thyroid lymphoma and breast, renal or lung metastases [1, 11].

Medical history and physical examination. History and physical examination of patients with thyroid nodules should comprise assessment of risk factors for malignancy.

The most incriminated and associated historical factors to malignancy are a history of childhood head and neck radiation therapy, total body radiation for bone marrow transplantation, exposure to ionizing radiation in childhood or adolescence (e.g. Chernobyl accident), familial thyroid carcinoma, or thyroid cancer syndrome (Cowden's disease, Carney complex, Werner syndrome, or MEN 2, as a risk diseases for medullary thyroid cancer) in a first-degree relative, rapid nodule growth [2, 6, 12].

Physical examination including inspection and palpation of the thyroid gland must be focused on nodules' location, size, texture, and examination of cervical lymph nodes. A thyroid nodule even harboring a thyroid cancer may be asymptomatic, but most of them are detected by the patient himself or medical practitioners as a lump in the anterior cervical region [3, 11-14]. The physical findings suggestive for malignancy are hard consistency and fixed nodule to surrounding tissue, vocal cord paralysis, and regional cervical lymphadenopathy [2, 4]. Rapid enlargement of a thyroid nodule may be associated with hemorrhage, especially if pain persists [3, 15]. The AACE/ACE/AME guideline mentions about a higher risk of cancer in nodules bigger than 4 cm in diameter, but more recent papers noted the highest malignancy risk in nodules <2 cm, meaning that size are inversely proportional to malignancy rate [13-15]. Large nodules provoke compression of underlying structures of trachea, esophagus, and recurrent laryngeal nerves leading to dyspnea or wheeze, dysphagia, and hoarseness correspondingly [2-4, 13-15].

Just as importantly, signs of hyperthyroidism or hypothyroidism also need to be extracted during thyroid nodules evaluation. Patients with hyperthyroidism have complaints about palpitations, heat intolerance, weight loss as opposed to increased appetite, frequent bowel movements, and anxiety, while in patients with hypothyroidism due to a slow metabolism rate are noticed fatigue, cold intolerance, constipation [2, 4, 9, 10, 16].

Paraclinical assessment and management

The present guidelines concentrate on three elements in thyroid nodules management – measurement of serum thyroid stimulating hormone (TSH), thyroid gland ultrasound, and fine-needle aspiration (FNA) of nodules [2-6].

Measurement of serum TSH is the initial laboratory test for all patients with thyroid nodules. Normal or elevated levels of TSH express a nonfunctioning nodule, and in large studies are associated with a higher risk of thyroid cancer [16, 17]. Low or suppressed levels are associated with hyperthyroidism and a radioisotope scan with iodine-123 or technetium-99m pertechnetate must be performed. Scintigraphically, the thyroid nodule can appear „warm" which means an isofunctioning nodule, „cold" which attests hypofunctioning nodule, and „hot" as a hyperfunctioning nodule. As stated by the guidelines, „hot" nodules do not require FNA and cancer vigilance, due to minor risk of malignancy, meanwhile nonfunctioning or „cold" nodules which combine clinical or/and ultrasound criteria, should be subjected to FNA [2, 4, 6]. Classically, malignancy rate in „hot" nodules has been reported to be about 0.34%, contested by the latest studies that found an increased malignancy incidence in „hot" nodules ranging between 10% and 34%, meaning that „hot" nodules need to be assessed in the same volume as to exclude a carcinoma, especially if they meet other relevant criteria [18, 19].

Other laboratory tests are not recommended for routine use [2, 4, 6]. Apart from the recommendation, not all health care professionals share this opinion. Serum thyroid hormones T_3 and T_4 are valuable in hyperthyroidism and hypothyroidism, particularly in their subclinical forms. T_3 and T_4 serum concentrations must be obtained in residents of iodine-deficient areas, and Republic of Moldova is considered such an area [16, 23]. Low values of T_3 and T_4 in conjugation with increased levels of TSH are related to malignancy [24, 25]. Determination of serum thyroglobulin (Tg), the storage form of iodinated thyroid hormones, can be a useful predictive biomarker to differentiate thyroid cancer and high levels of Tg are important in the adoption of the decision for surgery. Furthermore, the postoperatively elevated Tg levels are linked to a recurrent, persistent, or metastatic disease with a poor prognosis in cases of differentiated thyroid cancers [16, 20-22]. Calcitonin, another hormone produced by thyroid parafollicular C cells it is the single serum biomarker for detection of medullary thyroid cancer, which can be applied as a screening tool [26]. Acknowledging that antithyroid antibodies denote an autoimmune process including Hashimoto's thyroiditis or Graves' disease, the measurement of peroxidase antibodies, anti-thyroglobulin antibodies, and TSH receptor antibodies has an influential role. In addition to this, in a cross-sectional study and meta-analysis it was establish a higher prevalence of positive antithyroid antibodies in patients with carcinoma compared to those with benign nodules [27, 28].

Thyroid gland ultrasound is an essential tool in the evaluation and the first-line imaging investigation to stratify the risk of malignancy in thyroid nodules. Each guideline recommends a sonographic classification of thyroid nodules in an attempt to distinguish the malignant nodules before cytological evaluation or before follow-up. The ACR-TIRADS guideline compared to ATA and AACE/ACE/AME guidelines is widely accepted, with decreasing the number of FNA and has the highest accuracy in recognition of suspicious nodules [5, 29]. In 2017 The American College of Radiology, on the basis of breast reporting system, has introduced the Thyroid Imaging, Reporting and Data System (TI-RADS) that describe the ultrasound features of thyroid nodules such as composition, echogenicity, shape, margin, presence of echogenic foci and aid in calculation for a predictive score from TR1 - benign to TR5 - highly suspicious (Table 1) [5]. Although, the dimensions of thyroid nodules are not important for categorization, the cutoff size of nodules are taken into consideration for next step management.

Table 1. TI-RADS - Thyroid Imaging Reporting and Data System.

Composition (choose one)	Echogenicity (choose one)	Shape (choose one)	Margin (choose one)	Echogenic foci (choose one or more)
Cystic or completely cystic *0 points*	Anechoic *0 points*	Wider than tall *0 points*	Smooth *0 points*	None *0 points*
Spongiform *0 points*	Hyper- or isoechoic *1 point*	Taller than wide *3 points*	Ill-defined *0 points*	Large comet-tail artifact *0 points*
Mixed cystic and solid *1 point*	Hypoechoic *2 points*		Lobulated or irregular *2 points*	Macrocalcifications *1 point*
Solid or almost completely solid *2 points*	Very hypoechoic *3 points*		Extra-thyroidal extension *3 points*	Peripheral or rim calcifications *2 points*
				Punctate echogenic foci *3 points*
Summation of points to obtain a TI-RADS level				
0 points	*2 points*	*3 points*	*4-6 points*	*≥7 points*
TR1	TR2	TR3	TR4	TR5
Benign	Not suspicious	Mildly suspicious	Moderately suspicious	Highly suspicious
no FNA required	no FNA required	≥ 1.5 cm follow up, ≥ 2.5 cm FNA	≥ 1.0 cm follow up, ≥ 1.5 cm FNA	≥ 0.5 cm follow up, ≥ 1.0 cm FNA

Note: TR – TI-RADS category; FNA – fine needle aspiration.

Mainly reported patterns associated with a malignant nodule are hypoechogenicity, a taller-than-wide shape, lobulated or irregular margin, and microcalcifications [4, 12, 16]. It is noteworthy that these sonographic findings are more common to papillary thyroid cancers as the predominant type, and less typical to follicular or Hürthle cell tumors, medullary carcinoma and follicular variant of papillary thyroid cancer [4, 6, 16, 30].

Ultrasound is a valuable test in the evaluation of thyroid nodules, but it is also informative in the evaluation of cervical lymph nodes. None of the guidelines clearly recommends the exploration of cervical lymph nodes compartments, despite that their assessment adds precision to diagnosis. Papillary thyroid cancer has been found to metastasize in 30-65% to central lymph nodes (compartment VI) and in 3-44.5% to lateral lymph nodes (compartments III, IV), while regional lymph nodes metastases occur in less than 10% of follicular and Hürthle cell carcinomas [16, 31, 32].

Ultrasound elastography and color Doppler sonography are novel modalities that improve the diagnostic confidence of malignancies in thyroid nodules. Strain elastography or shear-wave elastography assesses tissue elasticity. The nodule stiffness indicates a malignant process. Some authors brought scientific evidence that this indicator can be used as an independent predictor for thyroid cancer and the elastography informativity is comparable to FNA [16, 33-35]. Color Doppler studies provide details about vascular architecture of thyroid nodules. Nodules with greater intranodular vascularity are more likely to be malignant than those with peripheral patterns [4, 34]. The existing guidelines do not support elastography and color Doppler modules for extensive use, regardless of the possibility of advancement in risk stratification of thyroid nodules and besides the fact that these tests are performed as a continuation of conventional ultrasound, and not as a separate investigation.

The routine use of cross-sectional imaging studies (CT, MRI) and 18-FDG PET scanning in evaluation of thyroid nodules are not approved. The American Association of Endocrine Surgeons (AAES) and ATA guidelines recommend preoperatively CT or MRI with intravenous contrast as an addition to ultrasound in patients with clinical suspicion of advanced locoregional thyroid cancer. Both CT and MRI project the images from the skull base to the mediastinum and are preferable in patients with confirmed thyroid nodules accompanied by vocal cord paralysis, positional dyspnea, mass fixation to surrounding structures, rapid enlargement of the nodule, and retrosternal extension of the thyroid gland [3, 6]. 18-FDG PET has a significant role in detecting recurrence of differentiated thyroid carcinoma and was estimated as a strong predictor of poor outcome in patients with metastases [6, 16].

As claimed by ACR-TIRADS guideline, thyroid nodules of 1 cm or larger with suspicious sonographic features require aspiration. Fine-needle aspiration is the unique method that provides the cytologic results of thyroid nodules. With the aim to unify data reporting and to obtain an interobserver agreement, in 2007 The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed. The system includes six general categories: TBSRTC I Nondiagnostic / Unsatisfactory ND/UNS; TBSRTC II Benign; TBSRTC III Atypia of undetermined significance / Follicular lesion of undetermined significance AUS/FLUS; TBSRTC IV Follicular neoplasm / Suspicious for a follicular neoplasm FN/SFN; TBSRTC V Suspicious for malignancy SUS, and TBSRTC VI Malignant. Cibas *et al.* in 2017 updated these categories due to the revised guidelines for the management of patients with thyroid nodules, the introduction of molecular testing as an adjunct to cytopathologic examination, and the reclassification of the noninvasive follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (Table 2). The revised version of TBSRTC reconsider as well the management options for thyroid nodules [36].

Nondiagnostic results (ND/UNS) occur in 5–15% of cases and nearby the updated TBSRTC recommendation, ATA, AACE/ACE/AME suggest resection for repeatedly nondiagnostic solid nodules and surgery or follow-up for cystic nodules [2, 4, 6, 36, 37]. Divergent opinions were published in several reports. Some researchers promote a conservative tactic because most often nondiagnostic nodules have benign outcomes and those with no suspicious features, mainly cystic, need only an ultrasound follow-up. Moon *et al.* advocated for resection of the ND/UNS nodules in repeated biopsies with at least one sonographic suspicious feature [37]. Raveh Gildin *et al.* divided the ND/UNS category in 3 subgroups – Blood, Thyrocytes and Cyst and showed that malignancy rates were different in each of them with the highest in the Blood subgroup succeeded by the Thyrocytes subgroup and the lowest in the Cyst subgroup, with the consideration of an individual subgroup approach [38].

Thyroid nodules are found to be benign on cytology in about 70% of all FNAs. The surveillance targets for these patients are to detect a missed malignancy, to observe nodule growth for the appearance of compressive symptoms or suspicious features [3, 6, 39]. The debatable point about benign nodules follow-up procedure, that none of the guidelines disclose is the exact length of this period, when one should stop the follow-up or to perform surgery to these nodules. Negro *et al.* in a 5-year monitoring study of benign nodules described the appearance of new nodule which require FNA, increase of nodule diameter > 50%, the appearance of compressive symptoms, and repetition of FNA on the existing nodule. These events occurred in 26.1% of patients, with more than one event occurring in the same patient in 27.7% of cases, summarizing that 71.9% of events were observed at 24- and 36-months of the monitoring process [40].

Table 2. The 2017 Bethesda System for Reporting Thyroid Cytopathology: Diagnostic Categories, Risk of Malignancy and Recommended Clinical Management.

Diagnostic categories	ROM if NIFTP is not cancer	ROM if NIFTP is cancer	Clinical management
I. Nondiagnostic or unsatisfactory Cyst fluid only; Virtually acellular specimen; Other (obscuring blood, clotting artifact, etc.).	5–10%	5–10%	Repeat FNA with ultrasound guidance
II. Benign Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.); Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context; Consistent with granulomatous (subacute) thyroiditis; Other.	0–3%	0–3%	Clinical and sonographic follow-up
III. Atypia of undetermined significance or follicular lesion of undetermined significance	6–18%	10–30%	Repeat FNA, molecular testing, or lobectomy
IV. Follicular neoplasm or suspicious for a follicular neoplasm Specify if Hürthle cell (oncocytic) type	10–40%	25–40%	Molecular testing, lobectomy
V. Suspicious for malignancy Suspicious for papillary carcinoma; Suspicious for medullary carcinoma; Suspicious for metastatic carcinoma; Suspicious for lymphoma; Other.	45–60%	50–75%	Near-total thyroidectomy or lobectomy
VI. Malignant Papillary thyroid carcinoma; Poorly differentiated carcinoma; Medullary thyroid carcinoma; Undifferentiated (anaplastic) carcinoma; Squamous-cell carcinoma; Carcinoma with mixed features (specify); Metastatic carcinoma; Non-Hodgkin lymphoma; Other.	94–96%	97–99%	Near-total thyroidectomy or lobectomy

Note: ROM - Risk of malignancy; NIFTP - Noninvasive follicular thyroid neoplasm with papillary-like nuclear features; FNA – fine needle aspiration.

Levothyroxine administration for TSH suppression is intended to decrease the volume of nodules and prevent the growth of existing or new formation of thyroid nodules. In clinical practice, this therapy registered a low efficacy with an increased risk of iatrogenic thyrotoxicosis, atrial fibrillation, and osteopenia. More beneficial to reduce nodule size is considered adequate dietary iodine intake (150 mg daily), especially in iodine deficiency areas [7, 9].

Some patients with benign nodules may complain of compressive symptoms, cosmetic concerns, and signs of hyperthyroidism due to an autonomously functioning thyroid nodule. Treatment options in these cases are surgery or minimally invasive techniques such as ethanol ablation (EA), image-guided thermal ablation (TA) procedures and radioactive iodine therapy (RAI). Among the currently available TA techniques are laser thermal ablation (LTA), radiofrequency ablation (RFA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU) that decrease nodule size by thermal coagulation necrosis induced by laser, radiofrequency, microwave, or high-intensity focused ultrasound respectively. TA is considered for nodules with a twice confirmed benignity on cytology, which does not exceed 3.0 cm in diameter. In case of cystic or predominantly cystic symptomatic nodules, initially is preferred EA with subsequent TA, if the nodule relapsed or the residual nodule has a solid component. TA should not substitute surgery in patients with compressive multinodular goiter, due to the need for multiple treatments and inadequate efficacy. In hyperfunctioning thyroid nodules, RAI may be considered, after decreasing hyperthyroidism with antithyroid drugs. Toxic multinodular goiter is not suitable for TA procedures [39, 41, 42].

Although, FNA differentiates benign from malignant thyroid nodules in an appropriate manner, in approximately 30% of patients persists diagnostic difficulties for nodules categorized with indeterminate cytology, comprising atypia of undetermined significance or follicular lesion of undetermined significance (TBSRTC III, AUS/FLUS) and follicular neoplasm (TBSRTC IV, FN/SFN) or Hürthle cell neoplasm (TBSRTC IV, HCN/SHCN) [42,43]. The AAES recommends for TBSRTC III nodules, in addition to the other guidelines, to reckon with clinical factors, radiologic features, and patient preference about repeat biopsy, molecular testing, diagnostic thyroidectomy, or observation [2, 4, 6]. Cytological assessment of a repeated FNA reclassifies this category in 60–65% and the nodules may be benign in up to 45% of cases. If the second cytological result is still indeterminate, diagnostic lobectomy provides the definitive pathological diagnosis [6, 39, 42, 43].

Molecular testing of the FNA samples is an innovative investigation introduced to refine the malignancy risk of cytologically indeterminate thyroid nodules. Genetic changes in thyroid carcinoma are developing directly in the thyroid tissue being nonhereditary – somatic mutations. Molecular

profiling includes point mutations in BRAF, RAS, RET, TERT, TP53, the fusion genes RET/PTC, PAX8/PPAR-γ, NTRK and/or micro-RNA (miRNA) expression [6, 43, 44]. The most studied genome for papillary thyroid cancer was performed by the Cancer Genome Atlas (TCGA) research network, which described the molecular portrayal of 496 papillary cancers in classical and follicular variants. Following this study, papillary thyroid cancers have a quite stable genome with genetic events recurring in a limited number of genes and a low mutation burden, hence one mutation rarely coexists in the same tumor, so the most common mutations determined in 70% of papillary cancers with a mutual exclusion are RET rearrangements or point mutations of RAS or BRAF protooncogenes [44, 45].

The commercially available tests, mainly in the USA are: ThyroSeq.v3 – the third version of ThyroSeq molecular test uses the next-generation sequencing technique of DNA and RNA to evaluate 112 thyroid-related genes that include point mutations, gene fusions, copy number alterations, and gene expression alterations to diagnose or rule out malignancy; Afirma Gene Sequencing Classifier and Xpression Atlas – uses a classifier to diagnose or rule-out malignancy according to gene expression based on RNA sequencing and operate the same RNA sequencing data to determine mutations and gene fusions in common with Xpression Atlas Panel; ThyGenX and ThyraMIR - ThyraMIR uses an algorithm of 10 microRNAs and ThyGeNEXT panel identifies DNA mutations and the RNA panel identifies the number of gene fusions [6, 45, 46].

Several limitations of using the molecular testing must be mentioned. The genome of follicular-derived thyroid carcinomas is highly variable among the cancer histological types. While the molecular changes of papillary thyroid cancers are almost understood, the molecular panel of follicular thyroid cancers is still unclear; moreover poorly differentiated and anaplastic cancers are often characterized by multiple co-occurring mutations that cannot be covered by available tests. Molecular tests are useless in diagnosis of Hürthle cell neoplasms determined by distinct molecular changes such as mitochondrial DNA mutations, point mutations recurring in atypical genes for thyroid cancer, and karyotype alterations in chromosomes 7, 5, 12. Some mutations, including those in RAS genes (HRAS, KRAS, NRAS) are present in malignant and nonmalignant thyroid neoplasms, invasive and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), unhelpful in differentiation benign from malignant nodules. In the studied literature, there is uncertain data about the negative predictive value of the tests because in 93% of long-term follow-up, sonographic, cytologic, and hystologic data of the unresected thyroid nodules are absent. Also. It is important to mention that if no mutations are confirmed, the malignancy should not be excluded [16, 45, 46].

Accepted options for patients with nodules cytologically categorized as TBSRTC IV are lobectomy and/or molecular testing. Cytological examinations of specimens cannot distinguish carcinomas from benign adenomas, due to the low possibility of assessing for capsular or vascular invasion of a nodule, even when a core-needle aspiration is performed. Molecular testing are limited for the same reasons for this category and has no influence on improvement of patient outcome such as survival or quality of life, or to reduce the number of thyroid surgeries [6, 16, 46, 47]. Diagnostic lobectomy is considered the only option to obtain definitive histology. For a malignant nodule, complete thyroidectomy is often indicated. It has been estimated that almost 60% of patients undergoing lobectomy for indeterminate cytology may be over- or undertreated at initial surgery [12, 48, 49]. In this context, in TBSRTC IV and even in TBSRTC V cytology, many surgical teams use intraoperative frozen section that is helpful in diagnosing malignancy and guiding decisions about initial surgical extent [6, 49].

Still it is not yet clear which nodules should be subjected to histology rather than cytology when taking into consideration the dimensions, number and suspicious features, as long as current guidelines are based on evaluation of single or dominant nodule in goiter between 1.0 to 4.0 cm.

In the medical literature, reviews, guidelines and studies, we can find a shallow approach of multinodular goiter, although each nodule in a multinodular goiter harbor an independent risk of malignancy. An algorithm of multinodular goiter management with clearest terms was published in 2014 by Lam *et al.* in reliance on three directions – thyroid function, mass effect, and nodule pathology with meaning of presence or absence of malignancy. In goiter associated with hyperthyroidism, compressive symptoms, and suspicion or confirmed malignancy, surgery was indicated. In cases of non-toxic, asymptomatic, and benign nodules within the multinodular goiter, the approach was reduced to observation [50].

Remains controversial the volume of thyroidectomies in III-VI TBSRTC categories and multinodular goiter. Most recent studies suggest as initial surgery of thyroid nodules with a hemithyroidectomy implies removing of the entire ipsilateral thyroid lobe and isthmus, including low-risk thyroid cancers to avoid recurrent laryngeal nerve injury or hypoparathyroidism with the advantage of no levothyroxine replacement [6, 7, 9, 12, 16, 36, 39, 50-52]. Beyond this concern, specialized centers register a low complication rate, <1% risk of permanent recurrent laryngeal nerve injury or hypoparathyroidism. It should be underlined that reoperating in an explored surgical field increase the risk to 3–10 times of permanent recurrent laryngeal nerve lesion or hypoparathyroidism [50].

In clinical practice, the perceptions of „low-risk" nodules may be dubious as a result of insufficient information for risk stratification provided by ultrasound and FNA reports [12, 51, 52]. The recommendation of hemithyroidectomy instead of total thyroidectomy when counseling patients is not clear as suggested in guidelines on the volume of surgery and the patient preference, implications for a long-term sonographic or cytologic surveillance, the potential for a completion thyroidectomy, need for postoperative thyroid hormone replacement should be considered. In addition,

clinicians and patients must establish the advantages of less extensive surgery against higher recurrence rate [50-53]. Wang *et al.* estimated that the risk factors for contralateral recurrent malignancy are: contralateral nodules misdiagnosed as benign, multifocality of primary carcinomas, capsular invasion, and Hashimoto's thyroiditis and may be reduced by performing frozen section examination [52].

Not insignificant are thyroid incidentalomas (TI). These are some of the most common incidental found nodules on imaging studies that include the neck CT, MRI, nuclear medicine, ultrasound, performed for other indications than thyroid evaluation. In 2015, the ACR formed the Incidental Thyroid Findings Committee to deduct a practical approach of managing incidentalomas [54]. Emerging from the fact that small and indolent nodules are more likely to be micropapillary carcinomas, the Committee stated that malignancy rate in TI depends on the techniques used to diagnose malignancy. Malignancy rate of TI detected by ultrasound is 12%, by CT and MRI ranges from 0% to 11% and with focal uptake on FDG-PET scans is higher 33-35%. The Committee recommends evaluation of TI with ultrasound in all cases, except in PET-avid lesions where thyroid ultrasound and FNA are considered. Some authors share the opinion that each thyroid incidentaloma, of any size, must be subjected to a comprehensive clinical, laboratory, instrumental, and cytological examination [55].

Conclusions

Thyroid nodules are common findings in general adult population with increasing prevalence. The primary concern that requires a careful assessment of each symptomatic nodule is the exclusion of malignancy. The initial evaluation of patients with thyroid nodules follow a risk stratification strategy that includes an exhaustive history and physical examination to identify risk factors, measurement of serum thyroid hormones, TSH, relevant biomarkers and neck ultrasonography to appreciate the size and suspicious features to select nodules to biopsy. Patients with benign nodules are subjected to active surveillance and in specific cases to minimally invasive techniques. Surgery is recommended for nodules that are suspicious for malignancy or malignant and is indicated for indeterminate compressive or any other symptomatic nodules. The main controversies appear in management of nodules with indeterminate cytology, low-risk cancers, multinodular goiters, hyperfunctioning nodules, and thyroid incidentalomas. The objective for a better management of patients with thyroid nodules is to identify the best individual treatment options and include the patient in the discussion with the multidisciplinary team regarding appropriate tactics, in terms of disease outcomes and quality of life, avoiding the dangers of overdiagnosis and overtreatment.

We have reviewed the guidelines recommendations, novel published data, and controversial points for health care professionals, to understand and provide efficient, personalized, and cost-effective management of patients with thyroid nodules in order to avoid automatic intensive testing and intervention and balancing each case from the patient expectations and demands.

Declaration of conflict of interests

There is no conflict of interest to declare.

Authors' contribution

CC - the collecting of data, the conception and drafting of the manuscript; AB - the critical revising of the manuscript for important intellectual content and the approval of the final version of the manuscript. Both authors - the analysis and the interpretation of data, approval of the „ready for print" version of the manuscript.

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