Systematic Review and Meta-Analysis

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Controversy regarding when clinically suspicious thyroid nodules should be subjected to surgery

Review of current guidelines

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Abstract

Background: The work-up of a thyroid nodule to diagnose malignancy is not always straightforward. There are various international thyroid societies each with their own guidelines on the approach to a thyroid nodule. The aim is therefore to determine whether a clinically suspicious thyroid nodule should be subjected to surgery.

Method: A review of various international thyroid society guidelines on their approach to a suspicious thyroid nodule.

Results: Sixty-two relevant articles were identified of which 4 current international thyroid guidelines, consisting of 6 different international societies, were reviewed. The commonalities of each of the thyroid society guidelines are imaging, with ultrasound, and cytopathology as the main diagnostic investigations. The description and the size of the nodule are the 2 most important factors on ultrasound; however, the guidelines vary in their recommendations whether to biopsy a suspicious thyroid nodule. An indeterminate group exists whereby thyroid nodules cannot be confirmed as malignant even with fine needle aspiration cytology (FNA). Although further investigations (Technetium-99m -sestamethoxyisobutylisonitryl scan, 18F-fluorodeoxyglucose positron emission tomography/computed tomography scan, and molecular testing) may assist in the diagnosis, there are limitations. There are differences in the guidelines whether suspicious nodules should be subjected to surgery.

Conclusion: Ultrasound and cytopathology are the 2 most appropriate investigations to diagnose whether a suspicious thyroid nodule is benign or malignant. The clinician needs to be aware of the differences between the guidelines from the various international thyroid societies, specifically concerning the indeterminate group of patients where a definitive diagnosis cannot be made. Management decisions should be discussed with a thyroid multidisciplinary team for a consensus decision whether or not to subject a patient with a suspicious thyroid nodule to surgery.

Abbreviations: AACE = American Association of Clinical Endocrinologists, ACE = American College of Endocrinology, ACR = American College of Radiology, AME = Associazione Medici Endocrinologi, ATA = American Thyroid Association, BTA = British Thyroid Association, CLIA/CAP = Clinical Laboratory Improvement Amendments/College of American Pathologists, CT = computed tomography, FDG-PET = 18F-fluorodeoxyglucose positron emission tomography, FNA = fine needle aspiration cytology, SestaMIBI = 99mTc-sestamethoxyisobutylisonitryl, TIRADS = Thyroid Imaging Reporting and Data System, U/S = ultrasound, UK = United Kingdom.

Keywords: cancer, cytology, indeterminate, nodule, thyroid, ultrasound

1. Introduction

The definition of a "thyroid nodule" is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding normal thyroid parenchyma.[1,2] Thyroid nodules occur in 4% to 8% of the general population.[3–6] Nodules detected with ultrasound and at autopsy increase the prevalence to 50% to 70%.[7–9] The majority of thyroid nodules are benign with malignancy in approximately 4% to 12% in palpable thyroid nodules as well as nonpalpable incidentalomas.[2,5,6,9–14]

2. Aim

The aim of this study was to determine whether a clinically suspicious thyroid nodule should be subjected to surgery.

3. Methods

This study is a review and comparison of various international thyroid society guidelines on their approach to a suspicious thyroid nodule. An electronic PubMed and Google Scholar search was performed, from 1994 until January 4, 2018, for guidelines relating to the management of thyroid nodules (refer to Fig. 1). The main search terms included "thyroid nodule guidelines," "thyroid nodule association guidelines," and "international thyroid guidelines." Ethical approval was not required, as it was a review of practice guidelines.

4. Results

Sixty-two relevant articles were identified of which 4 well-known current international thyroid guidelines were reviewed. The 4 guidelines consisted of 6 different international societies, including

Editor: Parag Parekh.

The author of this work has nothing to disclose and have no conflicts of interest.

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Medicine (2018) 97:50(e13634)

Received: 15 June 2018 / Accepted: 19 November 2018

http://dx.doi.org/10.1097/MD.0000000000013634

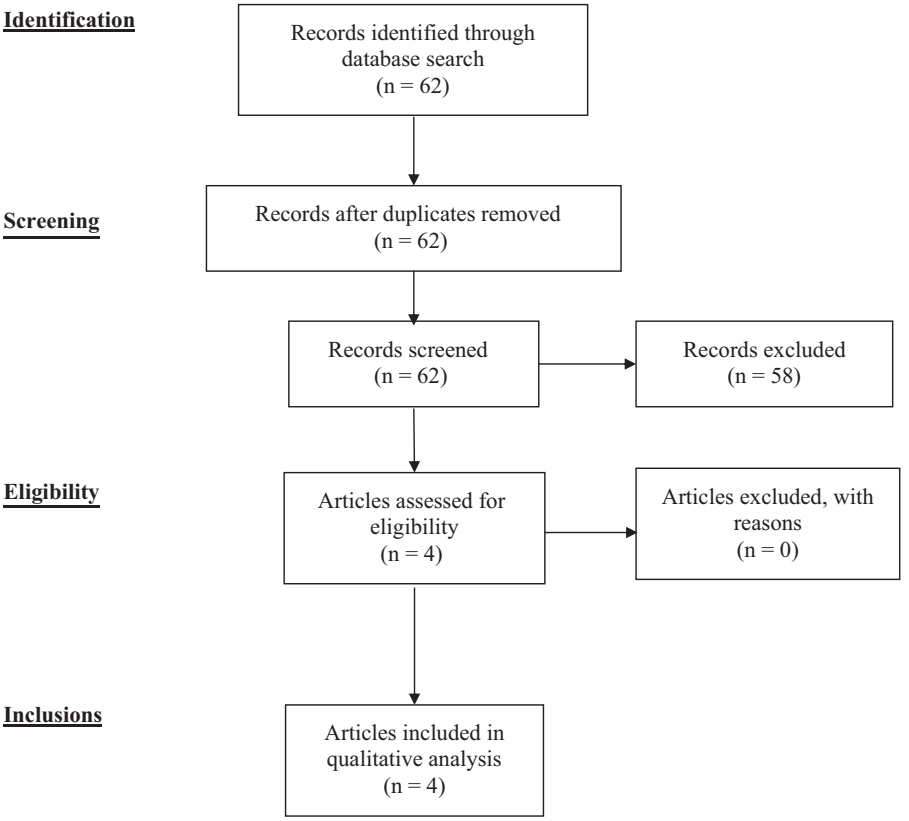

Figure 1. Flow diagram of review search.

American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), Associazione Medici Endocrinologi Medical guidelines (AME), British Thyroid Association (BTA), and European thyroid cancer consensus.

The main comparisons for the work-up of a suspicious thyroid nodule between the 6 international thyroid societies were tabulated into the 3 tables. The commonalities of each of the thyroid society guidelines are imaging, with ultrasound, and cytopathology as the main diagnostic investigations.

Table 1 compares the different ultrasound classification systems together with the risk of malignancy for each grade. Only the ATA and AACE/ACE/AME have malignancy risk recorded, which have subtle differences comparatively.

Table 2 compares the different ultrasound classification systems together with the recommended size indications for fine needle aspiration cytology (FNA). Each guideline recommends different size limitations for FNA of a thyroid nodule. As the ultrasound suspicion for malignancy increases, so the size indication for FNA decreases.

Table 3 compares the 2 commonly used cytology reporting systems, the Bethesda system for reporting thyroid cytopathology and United Kingdom-Royal College of Pathologists. The comparison includes the malignancy rate of each system. The 2 systems are closely matched with regard to the malignancy rate as well as the recommended management for each grade. The higher the grade, the greater the indication for surgery.

Table 1

Comparison of the risk of malignancy in the different ultrasound classification systems for suspicious thyroid nodules[1,15–17].

ATA		BTA		AACE/ACE/AME		ACR-TIRADS	
		Normal	Nd				
Benign	<1%	Benign	Nd	Low-risk	1%	TR1	Nd
Very low suspicion	<3%					TR2	Nd
Low suspicion	5–10%					TR3	Nd
Intermediate suspicion	10–20%	Indeterminate/equivocal	Nd	Intermediate-risk	5–15%	TR4	Nd
High suspicion	>70–90%	Suspicious	Nd	High-risk	50–90%	TR5	Nd
		Malignant	Nd				

AACE/ACE/AME = American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi, ACR-TIRADS = American College of Radiology -Thyroid Imaging Reporting and Data System, ATA = American Thyroid Association, BTA = British Thyroid Association, Nd = not defined.

Table 2

Comparison of ultrasound size indications for thyroid nodule fine needle aspiration[1,15–18].

ATA (2015)	BTA (2014)	AACE/ACE/AME (2016)	European consensus (2006)	ACR-TIRADS (2017)
	No FNA			
Benign. no FNA	No FNA	≥2 cm and increasing in size	≥1 cm	TR1. No FNA
Very low suspicion ≥2 cm				TR2. No FNA
Low suspicion ≥1.5 cm				TR3. ≥2.5 cm
Intermediate suspicion ≥1 cm	Any size	≥2 cm		TR4. ≥1.5 cm
High suspicion ≥1 cm	Any size	≥1 cm		TR5. ≥1 cm
	Any size			

AACE/ACE/AME = American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi, ACR-TIRADS = American College of Radiology -Thyroid Imaging Reporting and Data System, ATA = American Thyroid Association, BTA = British Thyroid Association, FNA = fine needle aspiration cytology.

5. Discussion

5.1. The work-up of a suspicious thyroid nodule for surgery

The indications for surgery in a thyroid nodule suspicious for malignancy are more complicated than benign conditions.[31] A dominant nodule, the largest nodule, in a multinodular goiter should be considered as significant as a solitary or single thyroid nodule.[32] Factors that increase the suspicion of malignancy include[6,13,15,16,18,33]:

(1) Age less than 20 or greater than 70 years;
(2) Rapid growth;
(3) Nodules larger than 4 cm in size (19.3% risk of malignancy);
(4) Firm and irregular consistency on palpation;
(5) Fixation of the nodule to adjacent tissues;
(6) Ipsilateral cervical lymphadenopathy;
(7) Vocal fold paralysis;
(8) History of neck irradiation;
(9) Family history of thyroid cancer.

There are various international guidelines on the work-up of a suspicious thyroid nodule for malignancy and when to operate or not.[1,15,16,18,34,35] The ATA, AACE, ACE, AME, BTA, and European thyroid cancer consensus have similarities.[1,15,16,18] All the guidelines do agree that ultrasound findings in conjunction with FNA results should be used to determine the need for surgery in a suspicious thyroid nodule. However, there are differences between the guidelines, including ultrasound and FNA criteria, which the clinician should be aware of.

5.2. Ultrasound of the thyroid

All patients in whom thyroid malignancy is suspected requires ultrasound of the thyroid nodules. Ultrasound can be very accurate in diagnosing malignancy in thyroid nodules, possibly even more so than cytology.[9,36] The ultrasound assessment can provide detailed information that may decide whether the nodule is benign or malignant. Two main advantages of a thyroid ultrasound examination are the description of features and determining the size of the nodule.

5.3. Significance of the description of thyroid ultrasound features

Ultrasound classification determines the indications for FNA. Certain ultrasound features indicate an increased risk of malignancy

Table 3

Malignancy rate and management comparison between the Bethesda system for reporting thyroid cytopathology and the United Kingdom-Royal College of Pathologists (2016) Thy numerical diagnostic categories[15,19].

Bethesda system for reporting thyroid cytopathology			UK-Royal College of Pathologists		
Bethesda category	Malignancy rate[15]	Management	Thy category	Malignancy rate	Management
I	1–4%	Repeat FNA with U/S guidance	Thy1	4.5–8.5%[20]	U/S assessment + repeat FNA
II	0–3%	Clinical follow-up	Thy2	<3%[21]	Correlate with clinical and radiological (U/S) findings
III	5–15%	Repeat FNA	Thy3a	9.5–43%[22–30]	Further investigation, usually U/S assessment + repeat FNA (Thy3a FNA on repeat sample requires Multidisciplinary Team discussion)
IV	15–30%	Surgical lobectomy	Thy3f		Diagnostic hemi-thyroidectomy
V	60–75%	Near-total thyroidectomy or surgical lobectomy	Thy4	68–70%[22,23]	Diagnostic hemi-thyroidectomy
VI	97–99%	Near-total thyroidectomy	Thy5	98–99%[15]	Therapy appropriate to tumor type, usually surgery for papillary or medullary thyroid carcinomas

FNA = fine needle aspiration cytology, Thy = thyroid, U/S = ultrasound, UK = United Kingdom.

in the nodule. The presence of microcalcifications in a solid nodule are associated with a 3-fold cancer risk.[13] Kim Criteria, which include marked hypoechogenicity, irregular or microlobulated margins, microcalcifications, and taller-than-wide shape (anterior-posterior diameter greater than the transverse diameter), have a high sensitivity for papillary thyroid cancer or medullary cancer.[15,37,38] Follicular thyroid cancer may present with different features such as isoechoeic or hyperechoic nodules without microcalcifications, regular smooth margins, and an irregular halo.[2,13,39,40]

Elastography is a dynamic ultrasound technique that some of the thyroid societies, such as AACE/ACE/AME, have incorporated in their ultrasound criteria assessment to diagnose thyroid malignancy.[3,13] Ultrasound elastography measures tissue stiffness. The stiffer the nodule, the more likely that the nodule is malignant. However, trials have reported mixed positive and negative predictive values compared with standard ultrasound.[2,41,42] There are also limiting factors to elastography such as calcifications resulting in a stiffer measurement and cystic nodules cannot be assessed with the elastography due to significant artefacts.[42]

Combining thyroid with cervical lymph nodes assessment under ultrasound has the highest sensitivity in diagnosing malignancy. Typical features suggestive of thyroid metastatic lymph node involvement include microcalcifications, peripheral or mixed vascularity, cysts, hyperechogenicity, and a round shape.[2,15,43]

Combinations of the ultrasound signs have been shown to increase the accuracy of the diagnosis and have resulted in the classification systems used by the different societies.[1,15,16] The ultrasound classification systems used by the ATA, BTA, and AACE/ACE/AME to describe a suspicious thyroid nodule are very similar. The ATA has 5 ultrasound categories (benign, very low suspicion, low suspicion, intermediate suspicion, and high suspicion), the BTA also has 5 categories (normal, benign, indeterminate/equivocal, suspicious, and malignant), and the AACE/ACE/AME has 3 categories (low-risk lesion, intermediate-risk, and high-risk). However, by comparing the ultrasound features of the different societies, some differences are noted but mostly comparable to each other. The BTA has a "normal" category, whereas ATA and AACE/ACE/AME do not. The ATA separates the ultrasound features into "benign," "very low suspicion," and "low suspicion," whereas the BTA and AACE/ACE/AME combines the similar findings into a category of "benign" and "low-risk lesion," respectively. The ATA category of "intermediate suspicion" is similar to the BTA "indeterminate/equivocal" category and the AACE/ACE/AME "intermediate-risk thyroid lesion" category. The ATA "high suspicion" category is comparable to the AACE/ACE/AME "high-risk thyroid lesion" category, which is also comparable but divided into 2 categories, "suspicious" and "malignant," according to the BTA.[16]

The Thyroid Imaging Reporting and Data System (TIRADS) is another well-known ultrasound classification system. TIRADS was first used in 2009 by Horvath et al.[44,45] Since then, it has been modified by the American College of Radiology (ACR) and published in 2017.[17] TIRADS classification was created in an attempt to standardize the reporting of results of thyroid ultrasound and stratify the risk of malignancy.

The ATA, BTA, and the AACE/ACE/AME ultrasound guidelines are pattern-based approaches, whereas the ACR-TIRADS is a points system.[1,15,16] The ACR-TIRADS points system is based on ultrasonographic features of composition, echogenicity, shape, margin, and echogenic foci. These points are then added and the 5 TIRADS levels are determined, TR 1 to TR 5. The higher the total, the more likely malignancy is present.

The significance for the clinician to compare the ultrasound classifications is to be aware of the risk of malignancy quoted for each classification, which guides further investigations. Comparison of the malignancy risk for each classification system is summarized on Table 1. Differences in classification systems may influence management of the nodule, such as a ATA "low suspicion" class is the equivalent of AACE/ACE/AME "low-risk lesion"; however the risk of malignancy in ATA is 5% to 10%, whereas the AACE/ACE/AME has the risk of malignancy at 1%.[1,16]

5.4. Significance of the size on ultrasound

Each of the Society recommendations uses the ultrasound features as well as the size of the nodule to determine whether FNA should be performed.[1,15–18] According to the ACR, the term "dominant nodule" should not be used, as it removes the emphasis from the ultrasound features.[17] The size cut-off/limits for each classification system is tabulated in Table 2. Once again, the significance of comparing the various society's thyroid nodule size (together with the descriptive ultrasound features) recommendations for FNA is for the clinician is to be aware that the indications for FNA are not the same. Size indications for FNA for each recommendation vary depending on the ultrasound classification system used. For example, a patient with a thyroid nodule of 1.2 cm and classified as "intermediate suspicion" under ATA, or an equivalent from the other societies, would be managed differently between each society. The ATA, BTA, and European consensus group guidelines would recommend FNA biopsy, whereas AACE/ACE/AME and ACR-TIRADS would not recommend FNA biopsy.

There are also other differences between the classification system recommendations. The AACE/ACE/AME recommends considering FNA for high-risk thyroid nodules $\leq$1 cm only when suspicious ultrasound signs are present, while nodules $\leq$5 mm should be monitored rather than biopsied.[16] The AACE/ACE/AME, BTA, and European group recommends that a history with high clinical suspicion of thyroid malignancy should be considered for FNA even if less than the cut-off size.[15,16,18] The ATA, AACE/ACE/AME, and the European group do not recommend FNA in a nodule that is hyperfunctioning as diagnosed on radioisotope scanning.[1,16,18]

5.5. Thyroid nodule biopsy

FNA is one of the important investigations for the work-up of a suspicious thyroid nodule. FNA is considered to be the most accurate in diagnosing the type of pathology in the thyroid nodule, with a sensitivity of 89% to 98% and a specificity of 92%.[46] FNA for thyroid nodules >4 cm (large nodules) may be less reliable in females than in males, but otherwise, the reliability of FNA is not usually affected by the size of the nodule >4 cm.[47–50] A core needle biopsy under ultrasound guidance is only recommended in cases when FNA diagnosis is difficult to obtain and when the histology would alter the management, for example, lymphoma.[15] Unfortunately, core needle biopsies do not provide additional information in diagnosing follicular tumors.[51] Open incisional biopsy is not recommended.[15]

The Bethesda system for reporting thyroid cytopathology is well known. In 2007, the Bethesda classification was created at the National Cancer Institute Thyroid FNA State of the Science Conference held in Bethesda, MD, where different cytopathology categories were decided upon.[39] The United Kingdom (UK) uses a different cytological classification, the Thy numerical diagnostic

categories as defined by Royal College of Pathologists.[15,52] The Bethesda system for reporting thyroid cytopathology (I-non-diagnostic/cystic fluid only; II-benign; III-follicular lesion/atypia or follicular lesion of undetermined significance; IV-follicular neoplasm or suspicious for follicular neoplasm; V-suspicious for malignancy; and VI-malignant) classification system correlates with the UK-Royal College of Pathologists (Thy 1-nondiagnostic, unsatisfactory, consistent with a cyst; Thy2-non-neoplastic; Thy3a-atypia/nondiagnostic; Thy3f-suggestive of follicular neoplasm; Thy4-suspicious for malignancy; and Thy5-malignant) description of the cytology categories. There are other cytopathological categories, also very similar, which are used by different thyroid societies.[16,53–55] The comparison of the risk of mortality and the recommended management between the Bethesda system for reporting thyroid cytopathology and UK-Royal College of Pathologists (2016) Thy numerical diagnostic categories can be found in Table 3. The risk of mortality and the recommended management is comparable between the 2 classifications.

In order for a thyroid nodule FNA specimen to be diagnostic, there has to be sufficient well-preserved epithelial cells with or without abundant colloid. For the FNA to be diagnosed as benign, there has be a minimum of 6 groups of benign follicular cells, each group composed of a minimum of 10 cells with or without colloid; or any FNA specimen that contains abundant colloid, even if less than 6 groups of follicular cells are present on 1 or more smears.[15,16,19,56] The benign FNA has the follicular cells arranged as macrofollicles and macrofollicle fragments.[19]

Thyroid nodule cytology considered as "nondiagnostic" or "unsatisfactory" requires the FNA to be repeated. Thyroid nodules diagnosed as benign on cytology do not require surgery.[1,15,18,19] However, the BTA does recommend that the clinical and ultrasound level of suspicion needs to be reviewed, and if there is a high level of suspicion for cancer, then a repeat ultrasound-guided FNA should be performed or the patient discussed with a multidisciplinary team.[15] Both ATA and AACE/ACE/AME agree that Bethesda V or Thy 4; and Bethesda VI or Thy 5 requires surgery. Bethesda V or Thy 4, cytology suspicious of malignancy, requires a near-total thyroidectomy or thyroid lobectomy (hemi-thyroidectomy). Bethesda VI or Thy 5, cytology indicating malignancy, requires thyroidectomy.[1,19] The BTA recommends surgery for Thy 5, but for Thy 4, repeating FNA or core biopsy under ultrasound guidance should be considered, and if the same result is obtained, then surgery is the next option.[15]

5.6. The indeterminate group

The indeterminate group, Bethesda III (atypia of undetermined significance or follicular lesion of undetermined significance)/IV (follicular neoplasm or suspicious for a follicular neoplasm) or Thy 3a/3f (neoplasm possible), are the categories that are not always straight forward. Cytological features do not allow for follicular carcinoma to be distinguished from follicular adenoma. Certain features may suggest carcinoma such as abundant follicular cells arranged in sheets, microfollicular or trabecular pattern, minimal background colloid, following which the FNA is categorized as follicular neoplasm (Bethesda IV or 3f).[19,55] Follicular carcinoma can only be diagnosed on histological samples where vascular or capsular invasion and cellular characteristics are assessed to diagnose malignancy.[5] Some papillary thyroid carcinomas may only have subtle nuclear and architectural changes, such as the follicular variant of papillary thyroid carcinomas.[19]

For the indeterminate categories, the European consensus group advocates for surgery.[18] The BTA recommends repeating FNA or core biopsy under ultrasound guidance, and if the result is still indeterminate, then the next option is surgery.[15] The AACE/ACE/AME recommends repeating the FNA while considering the ultrasound features and the clinical data for TIR 3A, and surgery or careful follow-up for TIR 3B.[16] The ATA recommends that an indeterminate result be correlated with the ultrasound and clinical findings in order to decide on close observation, repeating the FNA, or surgery.[1]

A technetium 99m-sestamethoxyisobutylisonitryl (sestaMIBI) scan can assist with the evaluation of a hypofunctioning nodule with a cytological diagnosis of follicular neoplasm (Bethesda IV). The sestaMIBI scan has up to 100% negative predictive value and will therefore exclude malignancy.[57]

18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT scan) is not a routine test for thyroid nodule work-up. It does not appear to be able to distinguish malignant from benign thyroid nodules. However, FDG-PET/CT scan does have a high negative predictive value of 95% to 100% and can therefore exclude malignancy.[6,58–60]

Molecular testing for the diagnosis of thyroid cancer may assist the clinician's decision on the appropriate management for the indeterminate group. Molecular testing on the FNA samples also has the same limitation as cytological interpretation, that is, an inadequate sample is required. However, molecular testing may be of benefit on FNA samples with insufficient quantity of cells for cytological interpretation.[1] BRAF has a high specificity for cancer but a low sensitivity, but using a group of mutation tests (BRAF, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3, PAX8/PPARc) increases the sensitivity to 44% to 100%.[61–63] Due to this variability of the sensitivity, the mutational analysis with a negative test may not assist the clinician to reliably exclude carcinoma. According to the ATA recommendation, molecular testing should only be performed in Clinical Laboratory Improvement Amendments/College of American Pathologists (CLIA/CAP)-certified molecular laboratories, or a similar international standard. The long-term outcome of using molecular testing to influence management decisions on thyroid nodules is still lacking and therefore has not been implemented as part of the routine work-up of a patient with possible malignancy.[1,16]

Although these special investigations can assist the clinician, a thyroid multidisciplinary team approach should always be considered. Also, these special investigations are not always available especially in low-resource countries. Thyroid ultrasound and/or cytology may be the only modalities available, and therefore, the clinician managing suspicious thyroid nodules should be aware of the differences between the different international thyroid society guidelines.

6. Conclusion

There is a stepwise approach for the work-up of a patient thyroid nodule; however, the order of the investigations may differ according to which recommendations are followed. Ultrasound and cytopathology are the 2 most appropriate investigations to diagnose whether a suspicious thyroid nodule is benign or malignant. The different thyroid society's criteria for the work-up of a thyroid nodule are similar, but there are differences that the clinician needs to be aware of. The concern is the indeterminate group of patients where a definitive diagnosis cannot be made. There are further investigations that may assist in the decision of

the risk that a suspicious thyroid nodule may contain malignancy, but the clinician needs to be aware of the limitations of these investigations. Management decisions should be discussed with a thyroid multidisciplinary team in order to make a consensus decision whether or not to subject a patient with a suspicious thyroid nodule to surgery.

Author contributions

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