Review Article

Current controversies in the management of patients with indeterminate thyroid nodules

Saad M. Alqahtani, MD.

ABSTRACT

يظل علاج عقيدات الغدة الدرقية غير المحددة خلويًا محل نقاش نظرًا لصعوبة إثبات الورم الخبيث. تحتوي معظم العقيدات على أنسجة حميدة بعد الجراحة، ولكن التقييم الدقيق لميلها للتحول الخبيث أمر بالغ الأهمية. لقد بحثت العديد من الدراسات في تأثيرات الأدوات المختلفة، بما في ذلك السمات السريرية والإشعاعية والخلوية، بالإضافة إلى الواسمات البيوكيميائية والجزيئية، على علاج هذه العقيدات غير المتجانسة. بشكل عام، تهدف الاستراتيجيات إلى علاج العقيدات الخبيثة وتجنب الجراحة غير الضرورية للعقيدات الحميدة بدون أعراض. في الوقت الحالي، لا توجد إرشادات واضحة للعلاج الأمثل للعقيدات الدرقية غير المحددة خلويًا لتحديد ما إذا كان يجب اختيار نهج تحفظي مع ملاحظة طويلة الأجل أو تدخل جراحي. وبالتالي، تم التوصية بأساليب شخصية. هناك حاجة لدراسات مستقبلية متعددة المراكز على نطاق واسع لتوضيح القضايا المثيرة للجدل. نظرًا لأن هذا الموضوع لم تتم تغطيته بشكل شامل بناءً على منشورات من منطقة الخليج، تهدف هذه المراجعة إلى تسليط الضوء على الخلافات المتبقية.

The management of cytologically indeterminate thyroid nodules remains debatable as their malignancy is difficult to establish. Most nodules have benign postoperative histology, but an accurate assessment of their proclivity for malignant transformation is crucial. Numerous studies have investigated the effects of various tools, including clinical, radiological, and cytological features, as well as biochemical and molecular markers, on the management of these heterogeneous nodules. Collectively, strategies aim to treat malignant nodules and avoid unnecessary surgery for asymptomatic benign nodules. Currently, no clear guidelines for the optimal management of cytologically indeterminate thyroid nodules exist to determine whether a conservative approach with long-term observation or surgical intervention should be selected. Thus, personalized approaches have been recommended. Large-scale multicenter prospective studies are needed to elucidate controversial issues. As this topic has not been comprehensively covered based on publications from the Gulf region, this review aims to shed light on remaining controversies.

Keywords: atypia of undetermined significance, follicular lesion of undetermined significance, Bethesda III, Bethesda IV, cytologically indeterminate thyroid nodules, follicular neoplasm, suspicious for a follicular neoplasm

Saudi Med J 2023; Vol. 44 (7): 633-639
doi: 10.15537/smj.2023.44.7.2023-0049

From the Department of Surgery, College of Medicine, Majmaah University, Al-Majmaah, 11952, Saudi Arabia

Address correspondence and reprint request to: Dr. Saad M. Alqahtani, Department of Surgery, College of Medicine, Majmaah University, Al-Majmaah, Kingdom of Saudi Arabia. E-mail: sm.alqahtani@mu.edu.sa
ORCID ID: https://orcid.org/0000-0002-2198-7970

Thyroid nodules (TNs), which are clinically palpable in approximately 5% of adults, are a common surgical condition.[1] Neck ultrasound (US), a simple and useful tool in the assessment of TNs, is by far more sensitive than clinical palpation in detecting TNs with a prevalence of 20-76%. Although the majority of TNs are benign and asymptomatic, the risk of malignant transformation ranges between 5 and 15%.[2] The risk of malignancy (ROM) in a solitary TN ranges from 2.7% to 33%; however, from 1.4% to 10% in a multinodular goiter. Barroeta et al[3] reported that the ROM is equal in one or 2 TNs >1 cm and decreases with ≥3 TNs.

Fine-needle aspiration cytology (FNAC) is a valuable diagnostic modality to evaluate TNs. It is characterized by high accuracy rates in detecting most benign and malignant conditions, such as papillary thyroid cancer (PTC) and anaplastic thyroid cancer. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which is commonly used, has a 97% sensitivity, a 50.7% specificity, a 3% false-negative rate, and a 0.5% false-positive rate.[4] However, 25% of all FNAC diagnoses are in a gray zone of uncertain cytology; they are referred to as "cytologically indeterminate TNs" (CITNs). In these categories, no or little colloid is detected, and it is difficult to distinguish malignant tumors (follicular variant of PTC and follicular carcinoma) from benign lesions (nodular adenomatous goiter and follicular adenoma).[5]

Cytologically indeterminate TNs comprise the categories Bethesda III, which is called atypia of

undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), and Bethesda IV, which is called follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN). Both Bethesda categories are known for their ambiguity and heterogeneity and the ROM is 5–15% in Bethesda III and 15-30% in Bethesda IV.[2,6] However, according to an updated TBSRTC version, the respective ROMs are 6-18% and 10–40% if noninvasive follicular thyroid neoplasm with papillary-like nuclear features is not considered a malignancy. When it is included in the malignancy risk assessment, the ROM increases to 10–30% in AUS/FLUS and 25-40% in FN/SFN nodules.[7] Notably, the actual ROMs in surgically excised AUS/FLUS nodules range from 6% to 48% and in FN/SFN resected nodules from 14% to 34%.[8]

Although 70-80% of CITNs have benign histology after surgery, they remain a clinically challenging group, and an accurate estimation of their ROM is critical.[4,5] In addition, being heterogeneous categories, their management remains difficult as to whether a conservative approach with long-term observation or surgical intervention should be chosen.[9] According to TBSRTC, the recommended strategy for Bethesda III TNs is a repeat FNAC, molecular testing, or diagnostic lobectomy, whereas in Bethesda IV TNs, the usual management is molecular testing or diagnostic lobectomy.[7]

Cytologically indeterminate TNs have been studied from a variety of perspectives, including clinical, radiological, cytological, biochemical, and molecular markers. In recent years, a personalized approach has been recommended for patients with CITNs.[10] The overarching aim is to make a diagnosis in order to treat malignant TNs while avoiding unnecessary invasive surgical procedures in asymptomatic benign TNs.[11] Table 1 summarizes different studies of CITNs in Saudi Arabia. Moreover, this is the first review from the Gulf region regarding the management of these specific nodules.

Clinical features. In general, a clinical assessment is the first step in TN evaluation. Compressive symptoms, rapidly growing nodules, male gender, a family history of thyroid cancer, age of presentation <20 years or >70 years, and previous radiation exposure, particularly during childhood, are all potential risk factors for malignancy. Thyroid nodules greater than 4 cm in size, fixed and hard nodules, the presence of cervical lymphadenopathy and distant metastases, and vocal fold immobility are signs suggestive of malignancy.[18]

It has been reported that male gender increases ROM in patients with CITNs, particularly when Hürthle cells are present.[5] This is confirmed by pooled data from a meta-analysis suggesting that male patients have a higher ROM than female patients.[5] Similarly, a retrospective study of 115 cases of AUS/FLUS found a significant correlation between gender and ROM, with men (64.3%) having a higher ROM than women (41.4%).[13] In contrast, some authors found no statistically significant relationship between ROM and gender in patients with CITNs.[19-21] Interestingly, Sorrenti et al[22] found that classical and follicular variants were more common in male patients, whereas more aggressive subtypes of PTC (tall cell, sclerosing, oncocytic) were more prevalent in female patients.

The effect of age as a risk factor for malignancy in CITNs is still a matter of controversy. Notably, some reports found that patients with ages more than 40 or 50 years had a higher ROM. Likewise, some studies have reported that the ROM increases at the extremes of age.[5] Based on univariate logistic regression analyses, Ho et al[23] concluded that AUS/FLUS patients with younger ages along with some US findings had a higher probability of undergoing surgery. However, other studies found no significant correlation between ROM and age.[2,13,19-21,24] Furthermore, it has been reported that older patients with TNs had a higher ROM.[25]

Repeat FNAC. When repeating FNAC in patients with CITNs, 76.0% had the same cytological diagnosis (Bethesda III or IV), whereas 7.4% of CITNs were reclassified as benign.[26] Furthermore, repeat US-guided FNAC revised the diagnosis to malignancy and suspicious for malignancy in 20% of patients who eventually underwent the proper procedure of total thyroidectomy (TT).[26] Another report showed that repeating FNAC in AUS/FLUS TNs results in a more definitive diagnosis in 56–68% of cases, whereas 15.6-48.6% of patients will have the same cytological AUS/FLUS diagnosis.[21] Based on a retrospective cohort study, it has been concluded that repeating FNAC in AUS/FLUS TNs is crucial and aids in discriminating benign from malignant TNs.[13] This was also supported

Disclosure. This study was supported by the Deanship of Scientific Research at Majmaah University, Al-Majmaah, Kingdom of Saudi Arabia. Project No.: R-2023-372

Table 1 - Different studies of cytologically indeterminate thyroid nodules in Saudi Arabia.

Study	Year	Bethesda category	Conclusions
Batawil and Alkordy[12]	2014	III & IV	US has limited accuracy or predictive value. Surgery is the recommended treatment for indeterminate thyroid nodules.
Alqahtani et al[13]	2017	III	Repeating FNAC has a significant role in discriminating benign from malignant nodules. No correlation between age or US variables and ROM. Men have a higher ROM.
Al Dawish et al[24]	2020	III	ACR TI-RADS displays accurate diagnostic performance in predicting malignancy.
Al-Hakami et al[14]	2020	III, IV, & V	The McGill Thyroid Nodule Score is helpful in preoperative decision-making in CITNs.
Alshahrani et al[15]	2021	III	Irregular margins, microcalcifications, multiple nodules, and hypoechogenicities increase the ROM.
Alqahtani et al[2]	2022	III & IV	None of the examined clinical or radiological features (ACR TI-RADS) contribute to the cancer risk stratification.
Alyousif et al[16]	2022	III & IV	ACR TI-RADS is significantly correlated with the FNAC outcome and is a useful tool in the absence of molecular tests for thyroid cancer.
Alqahtani et al[17]	2022	III	ACR TI-RADS does not help in cancer risk stratification. Repeated FNAC in AUS/FLUS nodules is recommended.

ACR TI-RADS: American College of Radiology Thyroid Imaging Reporting and Data System, AUS: atypia of undetermined significance, CITN: cytologically indeterminate thyroid nodule, FLUS: follicular lesion of undetermined significance, FNAC: fine-needle aspiration cytology, ROM: risk of malignancy, US: ultrasound

by the results of Chen et al[27] and Broome et al.[28] Furthermore, repeating FNAC in AUS/FLUS nodules >3 months after the initial diagnosis resulted in a higher diagnostic resolution (29).

A recent meta-analysis found that repeating FNAC helped reclassify two-thirds of the AUS/FLUS nodules into a more definitive category. Notably, 50% of the nodules were reclassified as benign with a negative predictive value of >96%. The authors of that study recommend repeat FNACs in the setting of AUS/FLUS TNs, especially in countries in which molecular testing is not available.[30]

Ultrasound features. Different medical societies have developed various US guidelines to reduce unnecessary FNACs and to better estimate cancer risk, but no single sonographic characteristic can appropriately discriminate benign from malignant TNs.[8,31-37]

Generally, TNs with hypoechogenicity, solid components, irregular margins, microcalcifications, taller than wider shapes, rim calcifications with small extrusive soft tissue components, and extrathyroidal extension all increase ROM by 70–90%.[8] Eisa et al[38] found that nuclear atypia along, with certain US features, is valuable in determining AUS patients with a higher ROM. Similarly, Barbosa et al[11] suggested that the 2015 American Thyroid Association (ATA) and American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) guidelines may help in the management of patients with CITNs.

A recent study comparing the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) with the ACR TI-RADS guidelines in the assessment of cancer risk of CITNs showed that both guidelines had comparable diagnostic performances for assessing the ROM of CITNs. Furthermore, the K-TIRADS aided in the assessment of the ROM of CITNs, particularly in PTC-prevalent areas.[39] A retrospective study of 110 AUS/FLUS cases concluded that US features and ACR TI-RADS scoring were ineffective in distinguishing benign from malignant lesions.[17] Other reports confirmed these findings,[2,21,40] Kotecka-Blicharz et al[4] demonstrated that US features were insufficient for determining the ROM of CITNs, and patients with CITNs were overtreated based on current diagnostic tools available in Poland.

A retrospective observational study showed that the pattern of malignancy in CITNs was well-differentiated, with low-risk follicular behavior and a favorable outcome regardless of nodule size. The authors of that study concluded that the extent of thyroidectomy (depending on tumor size and in the absence of other potential risk factors) contributes to overtreatment in the majority of patients.[41]

According to a recent cohort study of 652 CITNs, the vast majority (>90%) of cases were benign or low-risk malignant tumors. Therefore, the authors recommended lobectomy as an initial sufficient procedure independent of tumor size if other indications for total thyroidectomy were absent.[42] In contrast, in a meta-analysis of 3,494 patients with CITNs, the ROM was higher in nodules with a diameter of >4 cm.[5]

Of note, a negative 18F-fluorodeoxyglucose positron emission tomography/computed tomography result helps in determining a benign histopathology and can,

thereby, aid in avoiding unnecessary surgery due to its high negative predictive rate.[43]

Surgery. The extent of thyroidectomy (TT versus hemithyroidectomy [HT]) is determined by the presence of other factors such as clinical (history of radiation exposure), radiological (such as size >4 cm), and cytological features, as well as the molecular status. These factors should be considered in conjunction with other indicators such as the presence of comorbidities, hyperthyroidism, contralateral nodules, and ultimately the patient's preference.[41]

Some researchers argue that TT is required in the setting of CITNs because this allows the histopathologist to evaluate the whole gland and determine extrathyroidal extension, histologic variants of the tumor, and multifocality.[44-46] Other authors advocate that TT should be considered for patients with CITNs with worrisome features on US, size >3-4 cm, progressive growth of nodules, and in the presence of clinical risk factors.[25]

In contrast, HT is sufficient for lesions ≤1 cm in size.[44-46] According to the 2015 ATA guidelines, lobectomy alone is sufficient in most patients.[8]Similarly, Almquist and Muth recommend HT without lymph node dissection as the procedure of choice in patients with CITNs.[47] In contrast, Jooya et al[26] argue that HT is not the ideal procedure in patients with CITNs because it is either insufficient in the setting of malignant nodules or unnecessary in the setting of benign lesions. Schneider et al[48] found that 30% of patients with CITNs had an insufficient initial thyroidectomy (under- or overtreatment). The study by Kotecka Blicharz et al[4] concluded that the vast majority of patients were overtreated by using TT instead of lobectomy resulting in postoperative complications such as hypoparathyroidism, recurrent laryngeal nerve palsy, and hypothyroidism.

Some authors proposed "watchful waiting" as a strategic management option in certain patients with AUS/FLUS in the event of low epidemiological and radiological risk or according to the patients' preferences. It can also be considered in older FN/SFN patients with coexisting comorbidities and increased surgical risk.[47]

Molecular testing. Molecular testing is an effective tool for guiding CITN management.[9] Based on the ATA recommendations, molecular findings may influence the extent of thyroidectomy and the management of CITNs, especially whether surgical treatment or follow-up should be considered.[4] A study by Duick et al[49] demonstrated a significant reduction in diagnostic surgeries of CITNs after the implementation of the Afirma® Gene Expression Classifier test. Furthermore, molecular testing during FNAC may be valuable in the diagnostic workup of CITNs.[4] Unfortunately, the unavailability of these markers prevents their use in most centers. Furthermore, molecular testing increases both complexity and cost of management.[24]

Cytological subtypes. Several studies have concluded that the presence of nuclear atypia raises the ROM in both Bethesda III and IV categories.[38,50,51] Eisa et al[38] concluded that both ATA high-risk US findings and nuclear atypia are valuable in determining AUS patients with an increased ROM. Yoo et al[51] utilized different US risk stratification systems in their study (ATA, K-TIRADS, ACR TI-RADS, and European TIRADS). They also concluded that the categorization of AUS/FLUS nodules using such guidelines is helpful for determining the best treatment, particularly when combined with findings of the cytological subtype. Furthermore, the ROM of AUS/FLUS nodules with cytologic atypia is higher than that of AUS/FLUS nodules with architectural atypia, and surgery can be considered in such lesions with low or indeterminate suspicious features. However, the ROM of AUS/FLUS nodules with architectural atypia is low (12.5%), whereas the risk was found to be 50% in the high suspicion category.[51] Therefore, cytological subclassification in CITNs is a valuable adjunct tool in risk stratification for both diagnostic and therapeutic purposes.[50]

Biochemical markers. Several studies have been carried out to examine the roles of anti-thyroid antibodies and thyroid-stimulating hormone (TSH) in all cytological categories of TNs.[52-57] However, very few studies addressed the effects of these markers in CITNs.[44,55,58]

Adhami et al[58] found that anti-thyroid antibodies (thyroglobulin antibodies and thyroid peroxidase antibodies) and TSH levels were linked to higher ROM in patients with CITNs. Thyroglobulin antibodies and TSH may also be indicators of aggressive tumor biology. Thus, they can be utilized for diagnosis and prognosis. Another study found that preoperative thyroglobulin antibodies could be used to detect PTC in CITNs, potentially improving diagnostic accuracy. This suggests that thyroglobulin antibodies positivity may influence the clinical evaluation and subsequent patient selection for TT.[44] A recent retrospective study of 342 patients with AUS/FLUS found that a higher preoperative TSH level could be a valuable tool in predicting thyroid

malignancy.[10] Certain US features with TSH levels >4.5 mIU/L were associated with a higher ROM; however, this did not reach statistical significance.[24] This is supported by additional reports.[59,60] Low TSH levels, on the other hand, cause less thyroid epithelial cell differentiation and increase the risk of malignant cell transformation in 3 variants.[61] Another study showed a significantly lower PTC rate in patients with TSH levels <0.4 mU/L compared to patients with TSH levels >3.4 mU/L.[62]

In conclusion, the clinical management of CITNs remains controversial and challenging. Therefore, in recent years, personalized approaches have been recommended. Suspicious clinical, radiological, and cytological features, as well as biochemical data and molecular analysis, should be considered and weighted to stratify cancer risk and aid in the management of patients with CITNs. Furthermore, large collaborative multicenter prospective studies are needed to overcome these challenges.

Acknowledgment. *The author would like to thank Deanship of Scientific Research, Majmaah University, Al-Majmaah, Kingdom of Saudi Arabia for supporting this work under project number R-2023-372. In addition, he would like to thank Editage (www.editage.com) for the English language editing.*

References

1. McIver B. Evaluation of the thyroid nodule. *Oral Oncol* 2013; 49: 645-653.
2. Alqahtani SM, Alanesi SF, Mahmood WS, Moustafa YM, Moharram LM, Alharthi NF, et al. Clinical and ultrasonographic features in cancer risk stratification of indeterminate thyroid nodules. *Saudi Med J* 2022; 43: 473-478.
3. Barroeta JE, Wang H, Shiina N, Gupta PK, LiVolsi VA, Baloch ZW. Is fine-needle aspiration (FNA) of multiple thyroid nodules justified? *Endocr Pathol* 2006; 17: 61-65.
4. Kotecka-Blicharz A, Pfeifer A, Czarniecka A, Oczko-Wojciechowska M, Nożyńska E, Chmielik E, et al. Thyroid nodules with indeterminate cytopathology: a constant challenge in everyday practice. The effectiveness of clinical decisions using diagnostic tools available in Poland. *Pol Arch Intern Med* 2021; 131: 16117.
5. Trimboli P, Treglia G, Guidobaldi L, Saggiorato E, Nigri G, Crescenzi A, et al. Clinical characteristics as predictors of malignancy in patients with indeterminate thyroid cytology: a meta-analysis. *Endocrine* 2014; 46: 52-59.
6. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *Thyroid* 2009; 19: 1159-1165.
7. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017; 27: 1341-1346.
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016; 26: 1-133.
9. White MK, Thedinger WB, Dhingra JK. Long-term follow-up of cytologically indeterminate thyroid nodules found benign on molecular testing: A validation study. *OTO Open* 2022; 6: 2473974X221083542.
10. Kaliszewski K, Diakowska D, Rzeszutko M, Nowak Ł, Wojtczak B, Sutkowski K, et al. Assessment of preoperative TSH serum level and thyroid cancer occurrence in patients with AUS/FLUS thyroid nodule diagnosis. *Biomedicines* 2022; 10: 1916.
11. Barbosa TLM, Junior COM, Graf H, Cavalvanti T, Trippia MA, da Silveira Ugino RT, et al. ACR TI-RADS and ATA US scores are helpful for the management of thyroid nodules with indeterminate cytology. *BMC Endocr Disord* 2019; 19: 112.
12. Batawil N, Alkordy T. Ultrasonographic features associated with malignancy in cytologically indeterminate thyroid nodules. *Eur J Surg Oncol* 2014; 40: 182-186.
13. Alqahtani S, Alsobhi S, Alsalloum RI, Najjar SN, Al-Hindi HN. Surgical outcome of thyroid nodules with atypia of undetermined significance and follicular lesion of undetermined significance in fine needle aspiration biopsy. *World J Endocr Surg* 2017; 9: 100-103.
14. Al-Hakami HA, Al-Mohammadi R, Al-Mutairi R, Al-Subaie H, Al Garni MA. McGill thyroid nodule score in differentiating thyroid nodules in total thyroidectomy cases of indeterminate nodules. *Indian J Surg Oncol* 2020; 11: 268-273.
15. Alshahrani AS, Alamri AS, Balkhoyor AH, Mahzari MM, Alshieban SS, Majed PM. The prediction of malignancy risk in thyroid nodules classified as Bethesda system Category III (AUS/FLUS) and the role of ultrasound finding for prediction of malignancy risk. *Cureus* 2021; 13: e17924.
16. Alyousif H, Adam I, Alamin NA, Sid Ahmed MA, Al Saeed A, Hassoni AH, et al. The prevalence and associated predictors for Bethesda III–VI for reporting thyroid cytopathology in Royal Commission Hospital, Kingdom of Saudi Arabia. *Ther Adv Endocrinol Metab* 2022; 13: 20420188221122486.
17. Alqahtani SM, Al-Sobhi SS, Alturiqy MA, Alsalloum RI, Al-Hindi HN. The impact of thyroid imaging reporting and data system on the management of Bethesda III thyroid nodules. *J Taibah Univ Med Sci* 2022; 18: 506–511.
18. Mittal M, Ganakumar V, Shukla R, Kumar G. Thyroid nodule: approach and management. In: Agrawal NK (ed.) Goiter - causes and treatment. IntechOpen: London; 2020.
19. Teixeira GV, Chikota H, Teixeira T, Manfro G, Pai SI, Tufano RP. Incidence of malignancy in thyroid nodules determined to be follicular lesions of undetermined significance on fine-needle aspiration. *World J Surg* 2012; 36: 69-74.
20. Nagarkatti SS, Faquin WC, Lubitz CC, Garcia DM, Barbesino G, Ross DS, et al. Management of thyroid nodules with atypical cytology on fine-needle aspiration biopsy. *Ann Surg Oncol* 2013; 20: 60-65.
21. Park VY, Kim EK, Kwak JY, Yoon JH, Moon HJ. Malignancy risk and characteristics of thyroid nodules with two consecutive results of atypia of undetermined significance or follicular lesion of undetermined significance on cytology. *Eur Radiol* 2015; 25: 2601-2607.
22. Sorrenti S, Trimboli P, Catania A, Ulisse S, De Antoni E, D'Armiento M. Comparison of malignancy rate in thyroid nodules with cytology of indeterminate follicular or indeterminate Hürthle cell neoplasm. *Thyroid* 2009; 19: 355-360.
23. Ho AS, Sarti EE, Jain KS, Wang H, Nixon IJ, Shaha AR, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). *Thyroid* 2014; 24: 832-839.

24. Al Dawish M, Alwin Robert A, Al Shehri K, Hawsawi S, Mujammami M, Al Basha IA, et al. Risk stratification of thyroid nodules with Bethesda III category: the experience of a territorial healthcare hospital. ***Cureus*** 2020; 12: e8202.
25. Durante C, Pecce V, Grani G. Management of cytologically indeterminate thyroid nodules: primum non nocere. ***Pol Arch Intern Med*** 2021; 131: 16166.
26. Jooya A, Saliba J, Blackburn A, Tamilia M, Hier MP, Mlynarek A, et al. The role of repeat fine needle aspiration in the management of indeterminate thyroid nodules. ***J Otolaryngol Head Neck Surg*** 2016; 45: 51.
27. Chen JC, Pace SC, Khiyami A, McHenry CR. Should atypia of undetermined significance be subclassified to better estimate risk of thyroid cancer? ***Am J Surg*** 2014; 207: 331-336.
28. Broome JT, Cate F, Solorzano CC. Utilization and impact of repeat biopsy for follicular lesion/atypia of undetermined significance. World J Surg 2014; 38: 628-633.
29. Valerio E, Pastorello RG, Calsavara V, Porfírio MM, Engelman GG, Francisco Dalcin J, et al. Should we wait 3 months for a repeat aspiration in non-diagnostic/indeterminate thyroid nodules? A cancer centre experience. ***Cytopathology*** 2020; 31: 525-532.
30. Bayona A, Benavent P, Muriel A, Abuchaibe C, Sharpe SC, Tarasova V, et al. Outcomes of repeat fine needle aspiration biopsy for AUS/FLUS thyroid nodules. ***Eur J Endocrinol*** 2021; 185: 497-506.
31. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. ***J Clin Endocrinol Metab*** 2009; 94: 1748-1751.
32. Park JY, Lee HJ, Jang HW, Kim HK, Yi JH, Lee W, et al. A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. ***Thyroid*** 2009; 19: 1257-1264.
33. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. ***Radiology*** 2011; 260: 892-899.
34. Russ G, Bigorgne C, Royer B, Rouxel A, Bienvenu-Perrard M. [The Thyroid Imaging Reporting and Data System (TIRADS) for ultrasound of the thyroid.] (in French) ***J Radiol*** 2011; 92: 701-713.
35. Russ G, Royer B, Bigorgne C, Rouxel A, Bienvenu-Perrard M, Leenhardt L. Prospective evaluation of thyroid imaging reporting and data system on 4550 nodules with and without elastography. ***Eur J Endocrinol*** 2013; 168: 649-655.
36. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. ***J Am Coll Radiol*** 2017; 14: 587-595.
37. Modi L, Sun W, Shafizadeh N, Negron R, Yee-Chang M, Zhou F, et al. Does a higher American College of Radiology thyroid Imaging Reporting and Data System (ACR TI-RADS) score forecast an increased risk of malignancy? A correlation study of ACR TI-RADS with FNA cytology in the evaluation of thyroid nodules. ***Cancer Cytopathol*** 2020; 128: 470-481.
38. Eisa N, Khan A, Akhter M, Fensterwald M, Saleem S, Fananapazir G, et al. Both ultrasound features and nuclear atypia are associated with malignancy in thyroid nodules with atypia of undetermined significance. ***Ann Surg Oncol*** 2018; 25: 3913-3918.
39. Kang S, Kwon SK, Choi HS, Kim MJ, Park YJ, Park DJ, et al. Comparison of Korean vs. American thyroid Imaging Reporting and Data System in malignancy risk assessment of indeterminate thyroid nodules. ***Endocrinol Metab (Seoul)*** 2021; 36: 1111-1120.
40. De D, Dutta S, Tarafdar S, Kar SS, Das U, Basu K, et al. Comparison between sonographic features and fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. ***Indian J Endocrinol Metab*** 2020; 24: 349-354.
41. Cozzani F, Bettini D, Rossini M, Bonati E, Nuzzo S, Loderer T, et al. Thyroid nodules with indeterminate cytology: association between nodule size, histopathological characteristics and clinical outcome in differentiated thyroid carcinomas—A multicenter retrospective cohort study on 761 patients. ***Updates Surg*** 2021; 73: 1923-1930.
42. Valderrabano P, Khazai L, Thompson ZJ, Otto KJ, Hallanger-Johnson JE, Chung CH, et al. Association of tumor size with histologic and clinical outcomes among patients with cytologically indeterminate thyroid nodules. ***JAMA Otolaryngol Head Neck Surg*** 2018; 144: 788-795.
43. Piccardo A, Puntoni M, Treglia G, Foppiani L, Bertagna F, Paparo F, et al. Thyroid nodules with indeterminate cytology: prospective comparison between 18F-FDG-PET/CT, multiparametric neck ultrasonography, 99mTc-MIBI scintigraphy and histology. ***Eur J Endocrinol*** 2016; 174: 693-703.
44. Karatzas T, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Boutzios G. Thyroglobulin antibodies as a potential predictive marker of papillary thyroid carcinoma in patients with indeterminate cytology. ***Am J Surg*** 2016; 212: 946-952.
45. Calò PG, Medas F, Santa Cruz R, Podda F, Erdas E, Pisano G, et al. Follicular nodules (Thy3) of the thyroid: is total thyroidectomy the best option? ***BMC Surg*** 2014; 14: 12.
46. Kato MA, Buitrago D, Moo TA, Keutgen XM, Hoda RS, Ricci JA, et al. Predictive value of cytologic atypia in indeterminate thyroid fine-needle aspirate biopsies. ***Ann Surg Oncol*** 2011; 18: 2893-2898.
47. Almquist M, Muth A. Surgical management of cytologically indeterminate thyroid nodules. ***Gland Surg*** 2019; 8(Suppl 2): S105-S111.
48. Schneider DF, Cherney Stafford LMC, Brys N, Greenberg CC, Balentine CJ, Elfenbein DM, et al. Gauging the extent of thyroidectomy for indeterminate thyroid nodules: an oncologic perspective. ***Endocr Pract*** 2017; 23: 442-450.
49. Duick DS, Klopper JP, Diggans JC, Friedman L, Kennedy GC, Lanman RB, et al. The impact of benign gene expression classifier test results on the endocrinologist–patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. ***Thyroid*** 2012; 22: 996-1001.
50. Lim JXY, Nga ME, Chan DKH, Tan WB, Parameswaran R, Ngiam KY. Subclassification of Bethesda atypical and follicular neoplasm categories according to nuclear and architectural atypia improves discrimination of thyroid malignancy risk. ***Thyroid*** 2018; 28: 511-521.
51. Yoo WS, Ahn HY, Ahn HS, Chung YJ, Kim HS, Cho BY, et al. Malignancy rate of Bethesda category III thyroid nodules according to ultrasound risk stratification system and cytological subtype. ***Medicine (Baltimore)*** 2020; 99: e18780.

52. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. ***J Clin Endocrinol Metab*** 2008; 93: 809-814.
53. Muzza M, Degl'Innocenti D, Colombo C, Perrino M, Ravasi E, Rossi S, et al. The tight relationship between papillary thyroid cancer, autoimmunity and inflammation: clinical and molecular studies. ***Clin Endocrinol (Oxf)*** 2010; 72: 702-708.
54. Hosseini S, Payne RJ, Zawawi F, Mlynarek A, Hier MP, Tamilia M, et al. Can preoperative thyroglobulin antibody levels be used as a marker for well differentiated thyroid cancer? ***J Otolaryngol Head Neck Surg*** 2016; 45: 31.
55. Vasileiadis I, Boutzios G, Charitoudis G, Koukoulioti E, Karatzas T. Thyroglobulin antibodies could be a potential predictive marker for papillary thyroid carcinoma. ***Ann Surg Oncol*** 2014; 21: 2725-2732.
56. Golbert L, de Cristo AP, Faccin CS, Farenzena M, Folgierini H, Graudenz MS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. PLoS One 2017; 12: e0188123.
57. Boi F, Minerba L, Lai ML, Marziani B, Figus B, Spanu F, et al. Both thyroid autoimmunity and increased serum TSH are independent risk factors for malignancy in patients with thyroid nodules. ***J Endocrinol Invest*** 2013; 36: 313-320.
58. Adhami M, Michail P, Rao A, Bhatt CR, Grodski S, Serpell JW, et al. Anti-thyroid antibodies and TSH as potential markers of thyroid carcinoma and aggressive behavior in patients with indeterminate fine-needle aspiration cytology. ***World J Surg*** 2020; 44: 363-370.
59. Al Dawish MA, Alwin Robert A, Thabet MA, Braham R. Thyroid nodule management: thyroid-stimulating hormone, ultrasound, and cytological classification system for predicting malignancy. ***Cancer Inform*** 2018; 17: 1176935118765132.
60. Zafon C, Obiols G, Baena JA, Castellví J, Dalama B, Mesa J. Preoperative thyrotropin serum concentrations gradually increase from benign thyroid nodules to papillary thyroid microcarcinomas then to papillary thyroid cancers of larger size. ***J Thyroid Res*** 2012; 2012: 530721.
61. Gudmundsson J, Sulem P, Gudbjartsson DF, Jonasson JG, Masson G, He H, et al. Discovery of common variants associated with low TSH levels and thyroid cancer risk. ***Nat Genet*** 2012; 44: 319-322.
62. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, et al. L-thyroxine-treated patients with nodular goiter have lower serum TSH and lower frequency of papillary thyroid cancer: results of a cross-sectional study on 27 914 patients. ***Endocr Relat Cancer*** 2010; 17: 231-239.