Utility of Surgeon Performed Ultrasound Guided Fine Needle Aspiration Cytology for Diagnosis of Thyroid Nodules

Tiroid Nodüllerinin Tanısında Cerrah Tarafından Gerçekleştirilen Ultrason Kılavuzluğunda İnce İğne Aspirasyon Sitolojisinin Kullanışlılığı

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ABSTRACT

Background: The incidence of thyroid malignancy is increasing globally and this results in the growing number of patients facing increasing wait times for ultrasound (US) guided fine needle aspiration cytology (FNAC) for diagnosis. The objective of this study is to investigate the accuracy of surgeon performed US guided FNAC of thyroid nodules in the outpatient setting.
Methods: This was a retrospective cross-sectional study on patients who underwent US guided FNAC followed by thyroidectomy between July 2019 and September 2022. US TI-RADS grade, FNAC Bethesda category and final histology were obtained from medical records and analysed.
Result: There were 122 biopsy samples from 103 patients with a female gender preponderance of 89.3% and mean age of 46.5 years old. The majority of nodules biopsied were TI-RADS 4 and 5 (44.3% and 37.7%). Of the FNAC samples, 13.1% were non diagnostic, 27.9% benign, 14.7% atypia, 14.7% follicular neoplasm, 16.4% suspicious of malignancy and 13.1% were malignant. On final histology, adenomatoid nodules with nodular hyperplasia made up 82.5% of benign nodules and 94.9% of malignancies were papillary thyroid carcinomas (PTC). The overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 88.9%, 82.4%, 84.2%, 87.5% and 85.7% with higher accuracy rate (90.1%) when used in TI-RADS 5 nodules.
Conclusion: Surgeon performed US guided FNAC for thyroid nodules is feasible and can be done in the outpatient setting thereby reducing time taken to reach a diagnosis. Standardizing techniques and use of additional modalities such as elastography may improve yield and diagnostic rates.

Keywords: Thyroid, Fine Needle Aspiration Cytology, Ultrasound

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ÖZET

Amaç: Tiroid malignitesi insidansı küresel olarak artmaktadır ve bu durum, tanı için ultrason (US) kılavuzluğunda ince iğne aspirasyon sitolojisi (İİAS) için artan sayıda hastanın bekleme süreleriyle karşı karşıya kalmasına neden olmaktadır. Bu çalışmanın amacı, ayaktan tedavi ortamında tiroid nodüllerinde cerrah tarafından gerçekleştirilen US kılavuzluğunda İİAS'nin doğruluğunu araştırmaktır.
Yöntem: Bu çalışma, Temmuz 2019 ile Eylül 2022 tarihleri arasında US kılavuzluğunda İİAB yapılan ve ardından tiroidektomi uygulanan hastalar üzerinde retrospektif kesitsel bir çalışmadır. US TI-RADS derecesi, FNAC Bethesda kategorisi ve nihai histoloji tıbbi kayıtlardan elde edilmiş ve analiz edilmiştir.
Bulgular: Toplam 103 hastadan alınan 122 biyopsi örneğinde kadın cinsiyet oranı %89,3 ve ortalama yaş 46,5'tir. Biyopsi yapılan nodüllerin çoğunluğu TI-RADS 4 ve 5 idi (%44,3 ve %37,7). İİAB örneklerinin %13,1'i non diagnostik, %27,9'u benign, %14,7'si atipi, %14,7'si foliküler neoplazm, %16,4'ü malignite şüphesi ve %13,1'i malign idi. Nihai histolojiye göre, nodüler hiperplazili adenomatoid nodüller benign nodüllerin %82,5'ini oluştururken, malignitelerin %94,9'u papiller tiroid karsinomu (PTC) idi. TI-RADS 5 nodüllerinde kullanıldığında genel duyarlılık, özgüllük, pozitif prediktif değer, negatif prediktif değer ve doğruluk %88,9, %82,4, %84,2, %87,5 ve %85,7 olup daha yüksek doğruluk oranı (%90,1) elde edilmiştir.
Sonuç: Tiroid nodülleri için cerrah tarafından yapılan US kılavuzluğunda İİAB uygulanabilir ve ayakta tedavi ortamında yapılabilir, böylece tanıya ulaşmak için geçen süre kısalır. Tekniklerin standartlaştırılması ve elastografi gibi ek modalitelerin kullanılması verimi ve tanı oranlarını artırabilir.

Anahtar Sözcükler: Tiroid, İnce İğne Aspirasyon Sitolojisi, Ultrason

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INTRODUCTION

Thyroid nodules are common and the global incidence of thyroid carcinoma has been increasing over the past decade, almost doubling from 6.1/100,000 women and 1.9/100,000 men in 2012 to an estimated 10.1/100,000 women and 3.1/100,000 men in 2020 (1,2). This has largely been attributed to the advancement of technology in and the increase of usage of medical imaging resulting in an over-diagnosis of incidental thyroid nodules (3).

The American College of Radiology (ACR) in 2016 formulated the Thyroid Imaging, Reporting and Data System (TI-RADS) grading system to better aid clinicians in determining the malignant potential of nodules based on ultrasound (US) characteristics (4). Thyroid fine needle aspiration cytology (FNAC) was first described in 1962 and is currently regarded as the gold standard in obtaining pathological information from a thyroid nodule (5). The Bethesda System for Reporting Thyroid Cytopathology is a widely adopted reporting system for FNAC of thyroid nodules and each category is associated with an estimated risk of malignancy (6). The use of US for FNAC further improves on the adequacy and accuracy by enabling direct visualisation of the needle position during sampling of any nodule (5). Clinical judgement together with the use of ACR TI-RADS US grading and the Bethesda category from FNAC forms the basis of decision making in determining the next course of management of a thyroid nodule. In our centre, US guided FNAC of the thyroid has traditionally been under the purview of the department of diagnostic imaging. However in recent years, as with the rise in the number of patients and radiological procedures, waiting time for US guided FNAC appointments has been increasing. We believe that with surgeon-performed US guided FNAC in the bedside setting in the endocrine surgery outpatient clinic will provide convenience to patients and enable us to obtain cytological results earlier and therefore expedite intervention in cases which require surgery. This will also reduce the strain on the radiology department by reducing the number of cases requiring the procedure.

The purpose of this study is to look at the accuracy of surgeon performed US guided FNAC done in the bedside setting in the endocrine surgery clinic in detecting malignant thyroid nodules and to correlate malignancy risks of the TI-RADS grades and Bethesda categories in our centre.

METHODS

This retrospective cross-sectional study was performed in the Breast & Endocrine Surgery Unit of Hospital Queen Elizabeth II, a tertiary care institution in Sabah, Malaysia over a period of 38 months from July 2019 to September 2022. All patients aged 18 and above who have undergone surgeon-performed US guided FNAC and surgery were included in the study. Patients with a previous history of total thyroidectomy and patients without FNAC or histopathology (HPE) results were excluded. Ultrasound reports were retrieved from the Department of Radiology registry and cytological and histopathological reports were retrieved from the Department of Pathology registry. Data extracted from case files and documented onto a data collection sheet were age, gender, nodule US TI-RADS grade, FNAC cellularity yield, FNAC Bethesda cytological category and final histopathological subtype.

All patients were seen in the outpatient clinic of the Breast & Endocrine Unit with US reports and decisions for US guided FNAC made by the attending general or endocrine surgeon after clinical examination and review of ACR TI-RADS grade. All US guided FNACs were performed bedside in the clinic procedure room by either general or endocrine surgeons, or by general surgery registrars under supervision of surgeons. The US machines used were the LOGIQ-e and Versana Active (GE Medical Systems) with both systems using 12L-RS linear probes (GE Healthcare). Size of needle (23G or 22G) used were under the discretion of the performing doctor and a maximum of 4 attempts at any one time per nodule. The procedure was performed under US guidance with the needle parallel with the US probe. The use of either capillary method or suction method with a 10ml syringe was under the discretion of the performing doctor. After successful puncture and aspiration, adequacy of cellular material (7 clusters with at least 10 cells) was confirmed on-site by medical lab technologists from the Department of Pathology before specimens were despatched to pathologists. All thyroid cytological specimens were reported according to Bethesda categories. All surgeries were performed by general or endocrine surgeons from the Breast & Endocrine Surgery Unit and all surgical specimens were sent to the Department of Pathology for reporting of final histology.

Categorical variables were expressed as n (%). Chi-square test was used to compare variables within the benign and malignant groups. SPSS (IBM Corporation Released 2012, IBM SPSS Statistics for Windows, Version 21.0, IBM Corporation, Armonk, NY, USA) was used for statistical analysis and a p value of < 0.05 was accepted as statistically significant.

Ethical approval was obtained from the Medical Research and Ethics Committee (MREC) of Malaysia (approval reference number 22-02400-FUE (2) dated 21 December 2022) and conforms to the World Medical Association Declaration of Helsinki (June 1964) and its subsequent amendments.

RESULTS

A total of 122 biopsy samples were obtained from 103 patients, of which 15 patients had 2 separate biopsies and 2 patients had 3 separate biopsies. The mean age of patients were 46.5 years old and 89.3% of biopsies were from female patients (Table 1).

Table 1: Demographic data of patients

	Variables	***n (Total = 103)***	***%***
Gender	Male	11	10.7
	Female	94	89.3
Age	18-24	5	4.9
	25-34	8	7.8
	35-44	30	29.1
	45-54	23	22.3
	55-64	24	23.3
	65-74	11	10.7
	>75	2	1.9
Mean age 48.3 years (SD=13.6)			

Ultrasound TI-RADS grade 4 and 5 nodules constituted a majority (44.3% and 37.7%) of biopsied nodules (Table 2). There was an almost equal distribution of cellularity yield between the biopsied samples. Non diagnostic (Bethesda I) samples made up 13.1% of all biopsies, benign (Bethesda II) 27.9%, atypia of unknown significance (Bethesda III) and follicular neoplasm (Bethesda IV) 14.7% each, suspicious of malignancy (Bethesda V) 16.4% and malignant (Bethesda VI) 13.1%

The final histology of all biopsid nodules are shown in table 3, of which 63 (51.6%) were benign and 59 (48.4%) malignant. 82.5% of benign nodules were adenomatoid nodules with nodular hyperplasia and 94.9% of malignant nodules were Papillary Thyroid Carcinoma (PTC). There were only 1 case (1.7%) of Follicular Thyroid Carcinoma (FTC), Medullary Thyroid Carcinoma (MTC) and Hurthle Cell Carcinoma each from our samples. In our series, the risk of malignancy in TI-RADS 2, 3, 4, and 5 were 33.3%, 25%, 50% and 56.5% respectively (Table 4).

Table 2: Distribution of biopsy samples according to TI-RADS Grade, Cellularity Yield and Bethesda category

	Variables	***n (Total = 122)***	***%***
Nodule TI-RADS Grade	TI-RADS 2	6	4.9
	TI-RADS 3	16	13.1
	TI-RADS 4	54	44.3
	TI-RADS 5	46	37.7
FNAC Cellularity Yield	No Data	4	3.3
	Low	43	35.2
	Moderate	42	34.4
	Good	33	27.1
FNAC Bethesda Category	Bethesda I	16	13.1
	Bethesda II	34	27.9
	Bethesda III	18	14.7
	Bethesda IV	18	14.7
	Bethesda V	20	16.4
	Bethesda VI	16	13.1

TI-RADS – Thyroid Imaging, Reporting and Data System

Table 3: Distribution of nodules based on post-surgical histology

	Surgical Histology	*Subtype*	*n*	*(%)*
Benign (n=63)	Adenomatoid Nodules with Nodular hyperplasia		52	82.5%
	Hurthle cell adenoma		4	6.3%
	Hashimoto thyroiditis		3	4.8%
	Follicular adenoma		2	3.2%
	Colloid cyst		1	1.6%
	Calcified nodule		1	1.6%
Malignant (n=59)	Papillary Thyroid Carcinoma	Microcarcinoma	3	5.1
		Classical	42	71.2%
		Follicular	9	15.2%
		Tall Cell	2	3.4%
	Follicular Thyroid Carcinoma	Minimally Invasive	1	1.7%
	Hurthle Cell Carcinoma		1	1.7%
	Medullary Thyroid Carcinoma		1	1.7%

Table 4: Incidence of malignancy in final histology compared with TI-RADS grade

	TI-RADS 2, n (%)	*TI-RADS 3, n (%)*	*TI-RADS 4, n (%)*	*TI-RADS 5, n (%)*
Benign	4 (66.6)	12 (75)	27 (50)	20 (43.5)
Malignant	2 (33.3)	4 (25)	27 (50)	26 (56.5)
Total	6 (100)	16 (100)	54 (100)	46 (100)

TI-RADS – Thyroid Imaging, Reporting and Data System

Risk of malignancy of Bethesda V and VI biopsies were 80% and 100% (Table 5). There was a 50% risk of malignancy in both Bethesda III and IV categories. Bethesda II biopsies were 82.4% concordant with benign disease. Of the non-diagnostic biopsies, 81.2% were benign and 18.8% were ultimately malignant.

We used Galen and Gambino's method of calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (PPV) and accuracy. We excluded all Bethesda 1 biopsies as they are considered to be non-diagnostic and Bethesda III and IV as they are considered suspicious.

With the updated set of data, sensitivity was 88.9%, specificity was 82.4%, positive predictive value (PPV) was 84.2%, negative predictive value (NPV) was 87.5% and accuracy was 85.7% (Table 6).

A further analysis was performed by grouping the samples according to FNAC cellular yield. The sensitivity, specificity, PPV, NPV and accuracy of low, moderate and good cellular yields are shown in table 7. Results show a high accuracy of 84.2%, 83.7% and 90.1% throughout low, moderate and good FNAC cellular yields.

When the samples were grouped according to TI-RADS 4 and 5, sensitivity, specificity, PPV, NPV and accuracy increased with TI-RADS grade (Table 8).

Table 5: Incidence of malignancy in final histology compared to Bethesda category

	Bethesda I, n(%)	*Bethesda II, n(%)*	*Bethesda III, n(%)*	*Bethesda IV, n(%)*	*Bethesda V, n(%)*	*Bethesda VI, n(%)*
Benign	13 (81.2)	28 (82.4)	9 (50)	9 (50)	4 (20)	0 (0)
Malignant	3 (18.8)	6 (17.6)	9 (50)	9 (50)	16 (80)	16 (100)
Total	16 (100)	34 (100)	18 (100)	18 (100)	20 (100)	16 (100)

Table 6: FNAC result compared to Final Histology

		Final Histology	
		Benign	Malignant
FNAC	Benign	28 (TN)	6 (FP)
	Malignant	4 (FN)	32 (TP)

Sensitivity 88.9%, Specificity 82.4 %, PPV 84.2%, NPV 87.5%, Accuracy 85.7%, p <.001

PPV – Positive Predictive Value, NPV – Negative Predictive Value, p <.05 = statistically significant

Table 7: Sensitivity, Specificity, Predictive Values and Accuracy of FNAC of different cellular yields

	FNAC Benign		FNAC Malignant							
	HPE Benign	HPE Malignant	HPE Benign	HPE Malignant	Sensi-tivity	Speci-ficity	PPV	NPV	Accuracy	p value
Low	15	3	1	0	25	100	100	83.3	84.2	-
Moderate	8	1	28	6	96.6	57.1	82.4	88.9	83.7	.637
Good	4	1	16	1	94.1	80	94.1	80	90.1	.334

HPE- histopathological examination, PPV – Positive Predictive Value, NPV – Negative Predictive Value, p <.05 = statistically significant

Table 8: Sensitivity, Specificity, Predictive Values and Accuracy of FNAC of TI-RADS 4 and 5

	FNAC Benign		FNAC Malignant							
	HPE Benign	HPE Malignant	HPE Benign	HPE Malignant	Sensi-tivity	Speci-ficity	PPV	NPV	Accuracy	p value
TI-RADS 4	12	3	3	17	85	80	85	80	82.9	<.001
TI-RADS 5	7	1	1	13	92.9	87.5	92.9	87.5	90.1	<.001

HPE- histopathological examination, PPV – Positive Predictive Value, NPV – Negative Predictive Value, p <.05 = statistically significant

DISCUSSION

TI-RADS

The ACR TI-RADS was conceptualised and published in 2015 to serve as a guide to better stratify nodules based on US features and clinical recommendations that either warrant biopsy or serial US follow up (4). In our series, the malignancy rate of 33.3%, 24%, 50% and 56.5% in TI-RADS 2, 3, 4 and 5 were higher but still in accordance to reported incremental risks in each TI-RADS grade from the literature (<2% in TI-RADS 2, 2.1-5% in TI-RADS 3, 5.1- 20% in TI-RADS 4, >20% in TI-RADS 5) (7). The unusually high incidence of malignancy in TI-RADS 2 and 3 was due to a small sample size and is very likely not representative of true malignancy rates. Tappouni et al has highlighted that there was inter-reader variability for composition and echogenic foci and this may lead to up or down scoring of any particular nodule particularly when there is difficulty in differentiating between mixed solid cystic (1point) versus spongiform (0 points) and punctate echogenic foci (3 points) versus comet tail artifacts (0 points). During the course of our clinical practice, several cases whereby discrepancies were found between US findings of the attending surgeon with US reports, leading to re-discussions with the radiologist to repeat imaging and re-grading of TI-RADS score in these patients. Several meta-analyses have compared the diagnostic performance of different guidelines namely the ATA, ACR TI-RADS, KWAK TI-RADS and EU TI-RADS and all were found to be comparable with pooled sensitivity ranging from 83% to 94% and pooled specificity from 44% to 69% (8,9). The performance rates of these guidelines increase further when looking specifically into TI-RADS 4 and 5 nodules with pooled sensitivity rates of >90% and specificity rate of 61% (10). In accordance with ACR TI-RADS guidelines, we echo the need to FNAC all TI-RADS 4 and 5 lesions, and perhaps even lesions <1 cm in patients with high risk family histories or clinically suspicious lesions.

FNAC Technique

A meta-analysis by Song et al in 2015 found no statistical significance in the adequacy of smears and diagnostic performance between the 2 methods (12). However, a recent study by Wang et al reported better accuracy and specimen satisfaction rate when performing capillary method with a 25 gauge needle versus a 22 gauge needle in either aspiration or capillary method (13). A similar experience with the 25 gauge needle was also reported by Dong et al when comparing between 22, 23 and 25 gauge needles used with capillary method in their series (14). The cytological non-diagnostic rate was low (13.1%) in our series and well within the global reported incidences of 0.4% - 40.7% found in literature despite the variability in the use of needle with different gauge sizes and aspiration versus capillary method based on the preference of the performing surgeon. This is likely attributed to the availability of a trained medical lab technician on-site during the procedure to assess for adequacy of cells after each puncture attempt.

Bethesda III and IV Category Nodules

Bethesda III category nodules remain a challenge of management, especially more so in centres without molecular testing. There is usually some deliberation and variability in practice among surgeons who decide between US surveillance, repeat FNAC or surgery. A meta-analysis by Gao et al found that an increasing number of malignant features on US such as hypoechogenicity, irregular margins, microcalcifications, increase in size during follow-up, vascularity and disrupted rim calcifications increased the specificity of malignancy (48% with 1 feature, 54% with 2 features, 71% with 3 features) (15). Huang et al reported statistically significant associations between microcalcifications and taller-than-wide shape on US with risk of malignancy in Bethesda III and interestingly, nodules <1cm were more likely to be malignant than nodules that were larger (16). Whilst the sample size of our series was small, a malignancy rate of 50% in Bethesda III and 33.3% in Bethesda IV is higher than the published malignancy rate of the Bethesda consensus (5-15%, 15-30%). Zahid et al had also reported malignancy rates were similarly higher, between 15.7%-54.7% in Bethesda III and 16.8-64.2% in Bethesda IV, reported from 9 other studies (17).

In the event that there is non-concordance between clinical and US findings to FNAC Bethesda category III and IV nodules, we suggest a repeat FNAC or diagnostic hemithyroidectomy rather than surveillance, especially in nodules with high TI-RADS grade that are taller-than-wide and harbour microcalcifications as the risk of malignancy is higher.

Cytological Limitations

In a retrospective study by Özkara, there was a 42.5% risk of malignancy in Bethesda III nodules and 55.5% of tumours were FVPTC (18). FVPTC is a challenging entity as it may often be misdiagnosed as a follicular neoplasm or adenomatous nodule due to overlapping histologic features (19). This phenomena was seen in our series with 9 cases of FVPTC with a TI-RADS 4 and 5 grading on initial US but FNAC only showing Bethesda II - IV categories. Benign hyperplastic or adenomatous nodules and thyroiditis may also be misdiagnosed as malignant due to morphological features that mimic PTC, as shown from our series where 4 of 20 Bethesda V nodules were eventually benign hyperplastic or adenomatoid nodules. Aspiration from cystic lesions are often non-diagnostic, however have been reported as malignant false positives as some may share certain features of PTC such as spindle cells, nuclear enlargement, nuclear grooving and fine chromatin. There is emphasis that the diagnosis of PTC should only be reported if the smears were carefully scrutinised for true features of PTC such as nuclear crowding, intranuclear pseudoinclusions and papillary architecture of cystic papillary carcinoma (20). In a small series by Jambhulkar M. showed that by incorporating cell block preparation improved cellular yield and enabled clearer morphological interpretation than just cytological smear alone (21). In our centre, cell block preparation was only done in select cases whereby aspirates were highly haemorrhagic from vascular lesions. The use of cell blocks in low yield aspirates would likely reduce the rate of non-diagnostic smears resulting from insufficient cell clusters on smear cytology alone.

Aids To Improve FNAC Diagnosis of Thyroid Nodules

A 2014 meta-analysis by Trimboli et al included 8 studies investigating the reliability of elastography in evaluating thyroid nodules and reported a pooled sensitivity of 69%, sensitivity of 75%, PPV of 63%, NPV of 82% and accuracy of 73% (22). When used in accordance with US, sonographic features significantly associated with malignancy were microcalcifications, loss of halo sign, irregular margins and intranodular vascularity. This feature is available on most modern US machines, and although it requires some additional training, we believe it will be an invaluable adjunct on top of TI-RADS grade in determining the most suspicious nodule for FNAC. Other modalities to improve diagnosis of malignancy especially in indeterminate nodules range from immunohistochemistry stains like Galectin-3, BRAF mutation analysis, Gene Expression Classifiers, mutation/fusion panels to nuclear imaging such as FDG-PET/CT and MIBI-Scan (23). However many of the above tests are expensive and limited in availability confined to specialised laboratories. Galectin-3 with a good sensitivity of 83%, specificity of 85% and accuracy of 84% may represent the best viable alternate option based on cost to diagnostic accuracy ratio when compared to all of the non-invasive modalities above.

This study was a retrospective study and the sample size was rather small. Some samples were not included due to an incomplete data set from manual record keeping in our centre. A prospective study with a larger sample size would provide a more representative result and standardisation of technique and needle size may further improve cellular adequacy and quality of the cytological specimens.

CONCLUSION

Surgeon performed US guided FNAC has good accuracy in diagnosing malignancy in nodules with suspicious TI-RADS and Bethesda categories with higher malignancy rates from our study than initially published by their respective consensus papers. Nodules with a higher number of characteristic features of malignancy on US such as hypoechogenicity, taller-than-wide and microcalcifications increased the specificity of FNAC especially in cytologically indeterminate nodules. Usage of 25-gauge needle with capillary method may improve cellular yield and smear quality. Additional modalities such as elastography in combination with US and use of Galectin-3 may improve the diagnostic accuracy of FNAC and aid surgeons in deciding further management.

Conflict of interest

No conflict of interest was declared by the authors.

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