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The diagnostic role of FNA based on clinicopathological features in thyroid malignancy

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Abstract

Background Thyroid nodules are mostly benign lesions within the thyroid, with a small percentage being malignant. The decision for surgery is mainly based on the fine needle aspiration (FNA) cytology report, which is categorized into six categories from non-diagnostic to malignant. The accuracy of FNA is of utmost importance to minimize the complications due to misdiagnosis.

Methods In a retrospective study, we analyzed 310 patients who underwent thyroidectomy due to suspicious thyroid nodules with both FNA and histopathological results. We reviewed patient files, extracting demographic data, FNA results, and final histopathology reports and grouped them based on the size of the nodules. Sensitivity, specificity, and predictive values were calculated.

Results The average age of the patients was 42.9 ± 13.2 years, and the average size of the largest nodule diameter was 2.1 ± 1.89 cm. Histopathological evaluation of specimens obtained during surgery showed that 184 (59.4%) samples were malignant and 126 (40.6%) were non-malignant. The overall specificity was 96.8%, and the sensitivity was 89.6%, and the accuracy of FNA in diagnosing malignancy was 92.2%. Logistic regression analysis revealed that Bethesda classification (OR: 2.34; 95%CI: 1.73–3.16; $P < 0.001$), and also tumor size (OR: 2.02; 95%CI: 1.32–3.10; $P = 0.001$) exhibited a significant direct correlation with the capability of FNA in accurately diagnosing malignancy. The highest FNA accuracy of malignancy detection was among nodules above 3 cm (97.1%) while in nodules smaller than 1 cm the accuracy was 73.2%.

Conclusion FNA is a suitable diagnostic tool for detecting malignant nodules, while diagnostic capability varies with approaches to indeterminate FNA results. False positive and negative rates are crucial, with challenges in diagnosing malignancy in the context of multinodular goiter cases and smaller nodules.

Keywords Fine needle aspiration, Thyroid cancer, Thyroid nodule, Sensitivity, Specificity, Thyroidectomy, Surgical pathology

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Introduction

Thyroid nodules are discrete lesions within the normal thyroid parenchyma that are benign in 90% of the cases [1]. The reported prevalence of these nodules is 2–6% with palpation, 19–35% with ultrasonography, up to 68% with high frequency ultrasound, and 8–65% in autopsy [2, 3]. Despite the more common benign nature of these nodules, 5–10% of them are proven to be malignant lesions [4]. The importance of these nodules lies in their potential for malignancy and the high burden of thyroid cancer, which necessitates early detection and assessment of these nodules.

The initial symptoms of thyroid nodules include sensation of lump or foreign body in the throat, dysphagia, hoarseness, and pain, however, most patients are asymptomatic [5]. After a proper physical evaluation of the thyroid, a neck ultrasonography and a radionuclide thyroid assessment as well as a complete evaluation of the thyroid function including thyroid stimulation hormone, total and free thyroid hormones, and antithyroid peroxidase antibody levels are performed based on their indication to define the functionality and nature of the nodules [6]. The risk of malignancy (ROM) is then calculated and reported according to the American College of Radiology Thyroid Imaging Reporting and Data System or the American Thyroid Association guidelines regarding the sonographic features of the nodules [1, 7]. When the ROM is reported high enough by the radiologist, a fine needle aspiration (FNA) of the nodule is performed to define the type of pathology [6].

The recommendation on whether a patient undergoes surgery or not is based on the FNA cytology report which is obtained according to the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) [6]. These results are categorized as follows: (I) non-diagnostic, (II) benign, (III) atypia of undetermined significance (AUS) (5–10% ROM), (IV) follicular neoplasm (20–30% ROM), (V) suspicious for malignancy (50–75% ROM), and (VI) malignant. Non-diagnostic cytology occurs in samples that are not adequate [8, 9]. The patients with BSRTC category V and VI, along with persistent category III and IV (indeterminate categories) nodules are referred for thyroid lobectomy or near-total thyroidectomy [10]. Furthermore, there are some clinical features other than FNA results including large thyroid nodule, rapidly growing nodule and hyperthyroidism that can warrant thyroidectomy [11].

FNA is a cost-effective, simple and precise method to evaluate thyroid nodules, yet the false positive and false negative results can complicate the few cases that are misdiagnosed. By using clinical and sonographical features of the nodule, the rate of these errors could be remarkably decreased. Herein, we evaluated the accuracy and sensitivity of FNA results with regards to final pathology of dissected thyroid nodule and also the role of other clinicopathological features in malignant thyroid nodule diagnosis.

Materials and methods

Study design and setting

This retrospective study evaluated the records of 310 patients who underwent thyroidectomy due to clinically suspicious nodules between 2015 and 2020 at Namazi and Bu-Ali Hospitals, referral centers for thyroidectomy in Southern Iran. The inclusion criteria were cases with FNA and permanent (post-surgical) pathology results suspicious for thyroid malignancies. Cases with pathologies unrelated to the thyroid were excluded. Management of thyroid nodules follow The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults [11].

Data collection

A team of well-trained medical experts and general practitioners (S.K., R.Sh., P.M.) reviewed patient files, carefully extracting relevant information by referencing hospital archives and using specific disease codes. Data collected included patients' demographic information, pre-operative FNA results, post-operative histopathologic reports, the site and number of resected nodules and lymph nodes, and details of the surgical procedures.

Data analysis and outcome measures

Data were analyzed using SPSS version 26.0 software. Descriptive statistics were used to generate abundance graphs. The relationship between thyroid cancer features and related factors was evaluated using chi-square tests (χ^2) and independent sample t-tests. A p-value of less than 0.05 was considered statistically significant.

FNA results were categorized based on BSRTC as follows [10]:

- Category II: Non-malignant (ROM < 5%).
- Categories III and IV: Indeterminate (ROM between 5% and 50%).
- Categories V and VI: Malignant (ROM > 50%).

For the purpose of this study, indeterminate cases were further classified as either malignant or non-malignant based on clinical implications and practice, and analyzed separately.

The final (permanent) pathology results were considered definitive, and FNA results were compared accordingly to determine their malignant or non-malignant nature. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each category. The false positive rate (FPR) as 1 – PPV and false negative rate (FNR) as 1 – NPV were

also computed to assess the accuracy of FNA results in diagnosing thyroid malignancies.

We also grouped the cases based on the nodule location in unilateral, bilateral, isthmus, and their combinations groups and calculated the accuracy of FNA in detecting malignancy within each group by including indeterminate cases as malignant.

We further grouped our data based on the nodule size, which was measured through ultrasound evaluation, into three groups of under 1 cm, 1 to 3 cm, and above 3 cm, and compared the accuracy of FNA between these groups. As in previous studies, the 1 cm and 3 cm cut-offs were recommended to enhance the accuracy of malignancy diagnosis [12, 13]. The malignancy rate along with FNA sensitivity, specificity and accuracy were calculated.

Results

Population characteristics and features

During the study period, 310 cases of thyroid cancer were documented with both FNA and histopathology results. The average age of the patients was 42.9 ± 13.2 years (range: 13 to 92), with a predominance of females (257 cases, 82.9%) compared to males (53 cases, 17.1%). The average size of the largest nodule diameter was 2.1 ± 1.89 cm (range: 0.1 to 14 cm). Table 1 displays the location and size of thyroid nodules in the patients. As shown in Table 1, there was a significant difference in nodule size between the malignant and non-malignant groups.

Pathology results

Tables 2 and 3 show the FNA results among our study's patients in detail and based on BSRTC. Based on FNA results, 149 (48.1%) cases demonstrated only malignant components, 107 (34.5%) cases conveyed only non-malignant, and 54 (17.4%) were indeterminate or mixed. After considering indeterminate/mixed tumors with a malignant component in the malignant group, the frequencies were 150 (48.4%) cases of malignant, 108 (34.8%) cases of non-malignant, and 52 (16.8%) cases were indeterminate.

The histopathological evaluation of specimens obtained during the operation revealed the most frequent pathology was Papillary Thyroid Carcinoma (PTC), accounting for 160 (51.5%) cases. Based on our results, 184 (59.4%) of the samples were malignant, while 126 (40.6%) were non-malignant (Table 3).

We evaluated the association between the FNA results and the permanent histopathology results. Among the 150 cases identified as malignant based on FNA, 147 (98.0%) were confirmed as malignant by histopathology, while three (2.0%) were benign. Among the 108 cases identified as non-malignant by FNA, 17 (15.7%) were malignant and 91 (84.3%) were benign. Additionally, of the 52 cases classified as indeterminate by FNA, 20 (38.5%) were malignant and 32 (61.5%) were benign. Figure 1 demonstrates the distribution of malignancy among our FNA findings in our study.

We further examined the discrepancies between FNA and histopathology findings:

The three cases that were benign on histopathology but identified as malignant on FNA included: Multinodular goiter (MNG) labeled as PTC, MNG with squamous metaplasia labeled as PTC, Adenomatous goiter labeled as poorly differentiated carcinoma.

The 17 cases that were malignant on histopathology but identified as benign on FNA included: 12 cases of PTC, 2 cases of medullary carcinoma, 3 cases of the follicular variant of PTC. These cases were identified as Hashimoto thyroiditis, MNG, and colloid goiter in the histopathology results.

The 52 cases classified as indeterminate by FNA included 32 benign cases and 20 malignant cases, in which the FNA of these patients are demonstrated in Table 2. The pathology of these patients turned out to be adenomatous goiter, hurtle cell change, colloid goiter, MNG, Hashimoto, and lymphocytic thyroiditis.

Table 1 Location and size of thyroid nodules among patients undergoing thyroidectomy based on ultrasound evaluation

Variable		Value	Histopathology		*P*-value
			Malignant	Non-Malignant	
Largest diameter (cm)		1.5 [0.9–3.0]	1.2 [0.7–2.0]	3.0 [1.8–4.0]	**< 0.001**
Largest Size Group *N* = 223	< 1	56 (25.1)	51 (91.1)	5 (8.9)	**< 0.001**
	1 to 3	132 (59.2)	93 (70.5)	39 (29.5)	
	> 3	35 (15.7)	10 (28.6)	25 (71.4)	
Location *N* = 229	Bilateral	65 (28.4)	30 (46.2)	35 (53.8)	**< 0.001**
	Bilateral and Isthmus	15 (6.6)	8 (53.3)	7 (46.7)	
	Diffuse	1 (0.6)	1 (100)	0 (0)	
	Isthmus	7 (3.1)	6 (85.7)	1 (14.3)	
	Unilateral	120 (52.4)	90 (75)	30 (25)	
	Unilateral and Isthmus	21 (9.2)	20 (95.2)	1 (4.8)	

Values are presented as Median [Q1– Q3] or frequency (%)

Bold values indicate significant association

Table 2 Fine-needle aspiration evaluation among thyroidectomy patients

Group	Fine Needle Aspiration Finding	Frequency (%); *N* = 310
Malignant	Papillary thyroid carcinoma	142 (45.8)
	Medullar Carcinoma	3 (1.0)
	Poorly Differentiated Carcinoma	2 (0.6)
	Anaplastic Carcinoma	1 (0.3)
	Squamous Cell Carcinoma	1 (0.3)
Non-Malignant	Adenomatous Goiter	2 (0.6)
	Benign Follicular Nodule	5 (1.6)
	Colloid Goiter	3 (1.0)
	Multinodular Goiter	93 (30.0)
	Hashimoto	1 (0.3)
	Lymphocytic Thyroiditis	1 (0.3)
	Graves	2 (0.6)
Indeterminate or mixed	Atypia of undetermined significance	27 (8.7)
	Follicular Neoplasm	10 (3.2)
	Hurthle Cell change	5 (1.6)
	Neoplastic Nodule	3 (1.0)
	Multinodular Goiter + Hurthle Cell change	3 (1.0)
	Multinodular Goiter + Atypia of undetermined significance	1 (0.3)
	Atypical follicular lesion of undetermined significance	1 (0.3)
	Follicular Neoplasm + Atypia of undetermined significance + Hurthle cell change	1 (0.3)
	Follicular Neoplasm + Adenomatous Goiter	1 (0.3)
	Colloid Goiter + Lymphocytic thyroiditis	1 (0.3)
	Lymphocytic thyroiditis + Malignant change	1 (0.3)
BSRTC category	Benign (II)	108 (34.8)
	Atypia of undetermined significance (III)	32 (10.3)
	Follicular neoplasm (IV)	20 (6.5)
	Suspicious for malignancy (V)	1 (0.3)
	Malignant (VI)	149 (48.1)

BSRTC: Bethesda System for Reporting Thyroid Cytopathology

Diagnostic capability

The results of sensitivity and specificity analysis based on FNA and histopathological features are demonstrated in Fig. 2. We excluded indeterminate cases for the purpose of the overall analysis. The overall specificity was 96.8%, and the sensitivity was 89.6%, and the accuracy of FNA in diagnosing malignancy was 92.2%, with a PPV of 98.0% and a NPV of 84.2%.

When combining the indeterminate and non-malignant groups ($n = 160$), the sensitivity and specificity were 79.9% and 97.6%, respectively. The accuracy of FNA in diagnosing malignancy was 87.1%, with a PPV of 98.0% and a NPV of 76.9%.

When combining the indeterminate and malignant groups, the corresponding values changed as follows: The sensitivity and specificity changed to 90.8% and 72.2%, respectively. The accuracy of FNA in diagnosing malignancy changed to 83.2%, with a PPV of 82.7% and a NPV value of 84.3%.

We further analyzed the correlation of various factors with the concordance between FNA and histopathology results. Our findings indicate that age and gender did not show a significant association with FNA's ability to correctly diagnose malignant and non-malignant cases ($P = 0.34$ and 0.24, respectively). However, bilateral involvement and the size of the nodule were significantly associated with FNA's capability to correctly diagnose malignant and non-malignant cases ($P = 0.01$ and 0.03 respectively).

We further analyzed our data based on logistic regression analysis, to demonstrate the capability of correct diagnosis of malignancy by FNA, based on our variables. Our results revealed that Bethesda classification exhibited a significant direct correlation (OR: 2.34; 95%CI: 1.73–3.16; $P < 0.001$), indicating that higher Bethesda score is associated with a more accurate FNA diagnosis. Also, tumor size demonstrated a significant direct correlation (OR: 2.02; 95%CI: 1.32–3.10; $P = 0.001$), with the capability of FNA in accurately diagnosing malignancy in tumors with larger sizes.

Furthermore, based on the cut-off points for the size groups in cases with available data ($n = 223$) and by including indeterminate cases as non-malignant, we demonstrated that the larger the size of the nodule, the higher capability of FNA in achieving a correct diagnosis

Table 3 Histopathological findings from thyroidectomy patients in Southern Iran

Group	Subgroup			Frequency (%); *N* = 310
Malignancy	Total			181
	Differentiated	Derived From Follicular Epithelioma	Papillary thyroid carcinoma Conventional	157 (50.6)
			Hurtle Cell Carcinoma	1 (0.3)
			Papillary thyroid carcinoma Follicular Variant with Capsular Vascular Invasion	12 (3.9)
			Follicular Thyroid Carcinoma	2 (0.6)
		Derived From Parafollicular Epithelioma	Medullary Thyroid Carcinoma	7 (2.3)
	Undifferentiated	Anaplastic Thyroid Cancer		2 (0.6)
Non-Malignant	Total			100
		Colloid Goiter		4 (1.3)
		Follicular Adenoma		4 (1.3)
		Multinodular Goiter		78 (25.2)
		Hashimoto		4 (1.3)
		Hurthle Cell Adenoma		1 (0.3)
		Adenomatous Goiter		4 (1.3)
	Lymphocytic Thyroiditis			1 (0.3)
	Hyperplastic Nodule			1 (0.3)
	Cystic Fluid			1 (0.3)
	Graves			2 (0.6)
Mixed	Papillary thyroid carcinoma + Follicular Carcinoma			1 (0.3)
	Papillary thyroid carcinoma + Multinodular Goiter			1 (0.3)
	Hashimoto + Hurthle Cell Adenoma			2 (0.6)
	PTC and Anaplastic carcinoma			1 (0.3)
	Multinodular Goiter + Hyperplastic nodule			3 (1)
	Multinodular Goiter + Squamous Metaplasia			1 (0.3)
	Multinodular Goiter + Lymphocytic thyroiditis			6 (1.9)
	Multinodular Goiter + Hashimoto			7 (2.3)
	Colloid goiter + Hyperplastic nodule			1 (0.3)
	Colloid goiter + Hyperplastic nodule + Lymphocytic thyroiditis			1 (0.3)
Nonthyroidal	Parathyroid Adenoma	Non-Malignant		1 (0.3)
Premalignant	Follicular Neoplasm (non-invasive follicular thyroid neoplasm with papillary like nuclear features)			4 (1.3)

about the nodule malignancy in regards to sensitivity and accuracy (Figs. 2 and 3).

Discussion

Thyroid nodules are infrequently labeled as malignant and accurately diagnosing this small proportion can prevent excessive morbidity as well as undertreatment in patients. FNA is the gold standard in diagnosing malignant thyroid nodules before surgery and determines the subsequent steps in managing patients with thyroid nodules [6]. We demonstrated that thyroid FNA is relatively effective in predicting malignant nodules, while also demonstrating the effect of clinicopathological features such as size and location of the thyroid nodule in thyroid cancer diagnosis in patients who are candidates for thyroidectomy.

The sensitivity and specificity of FNA can be calculated under two conditions regarding indeterminate results. Hsiao et al. considered both indeterminate and malignant FNA results with malignant final pathology as true positive results in their meta-analysis of 16,597 patients, calculating sensitivity and specificity to be 85.6% and 71.4%, respectively [14]. The rationale behind this calculation is based on the subsequent evaluations that patients with indeterminate nodules undergo, which can reveal the malignant nature of the nodule and the need for surgery. In our study, 38.5% ($n = 20$) out of 52 indeterminate FNA results were found to be malignant in final pathology. By considering indeterminate FNA results as malignant, the sensitivity and specificity were 90.8% and 72.2%, respectively. Conversely, by including indeterminate FNA cases in the non-malignant group, the specificity rose to 98% while sensitivity dropped to 80%. In this scenario, the PPV and accuracy are higher (98% and 87% vs. 83% and 83%, respectively) as negative results are detected more accurately. Furthermore, Pediatric

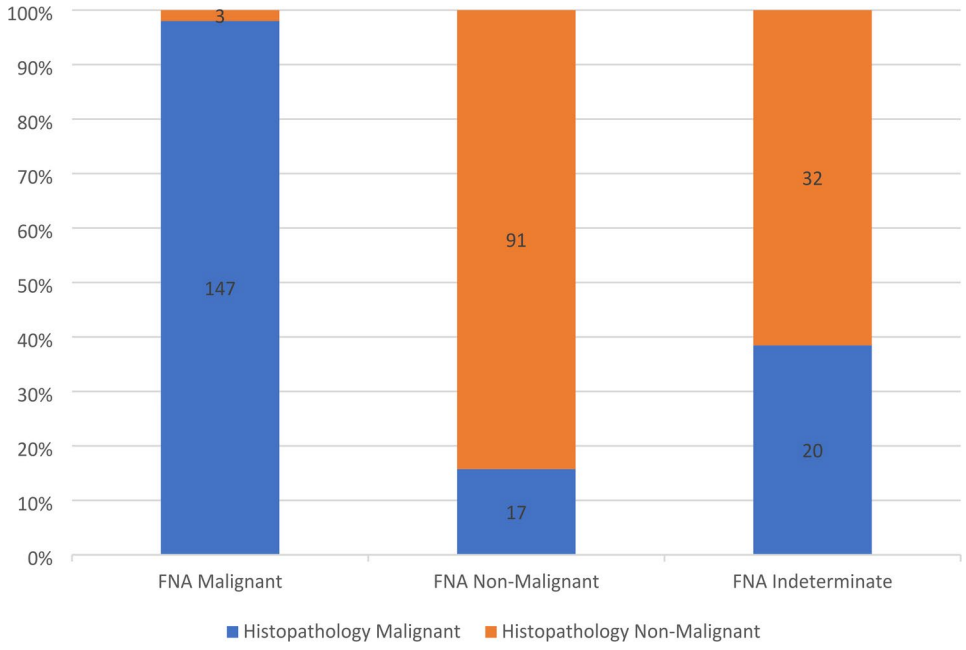


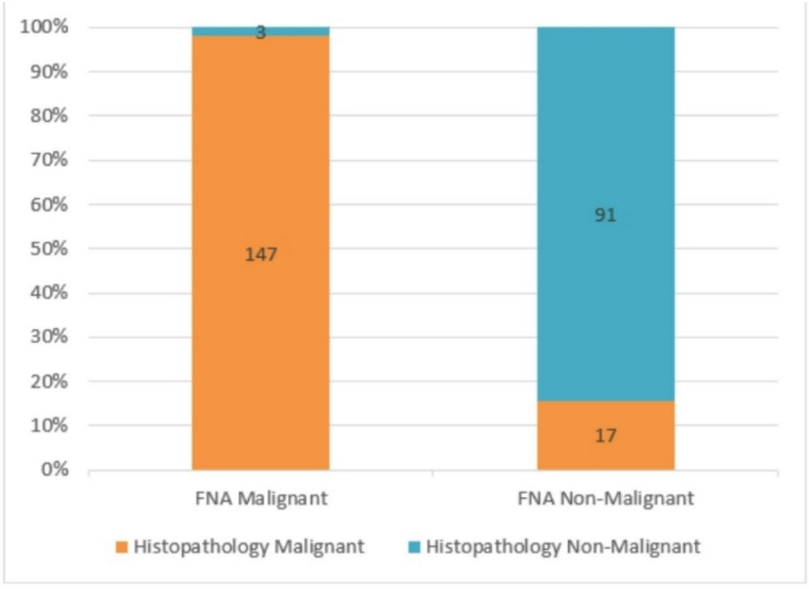
Fig. 1 Thyroid malignancy diagnosis by thyroid FNA in thyroidectomy patients

patients with indeterminate FNA result have a higher rate of malignancy than adult patients [15]. In spite of this difference, Canberk et al. showed that thyroid FNA sensitivity, specificity and accuracy are lower in pediatric patients and they change same as our results by including indeterminate cases as malignant [16]. There is no preference between sensitivity and specificity for determining the diagnostic value of FNA, since it functions both as a screening method for highly suspicious nodules and as a critical decision point for confirming malignancy and deciding on surgical intervention. Moreover, the holistic picture should be considered to avoid bias and misinterpretation. Therefore, including the indeterminate cases as non-malignant which provides a higher accuracy is more favorable.

The false positive and, more importantly, false negative results are of utmost importance as the FNA has a central role in pre-operation evaluation of patients with thyroid nodules. Zhu et al. reported a rate of less than 5% in most studies and 7.5–21% in some study series for false negative rate [17]. In our study the FNR and FPR are 23% and 2% respectively. However, our cases were all indicated for thyroidectomy and their FNA results were merely a proportion of their data, and this discordance between other studies could be due to the difference in the population of selected patients, and eligibility for surgical resection. The 17 false negative cases are all labelled as MNG which is recently shown to have higher rates of malignancy and FNA is not an adequate method to differentiate malignant lesions from benign lesions in these instances [18, 19]. Moreover, 50% of false negative cases with available pathology size have a PTC with largest diameter less than 10 mm which is considered papillary thyroid microcarcinoma, a highly missed malignancy and more prevalent in MNG cases [13]. On the other hand, there are 35 false positive cases in our study, mostly (32 cases) indeterminate cases, which underwent surgery due to their clinical features. 46% of the cases ($n = 16$) are reported as AUS and 34% of the cases ($n = 12$) are reported as hurthle cell (follicular neoplasm) which are both considered to have an ROM of under 50%. The three definite cases of false positive diagnosis consist of two PTC cases and one case of poorly differentiated carcinoma in the FNA, and the final pathology results include one case of MNG, one case of adenomatous goiter (another term to describe MNG) [20], and one case of mixed MNG and squamous metaplasia. Squamous metaplasia can be a precursor to a more aggressive form of PTC and this cancer is more prevalent in MNG cases, plus the presence of PTC can be overestimated in these cases due to large diameter in two of them (larger than 3 centimeters) [13, 21]. These false results can be avoided by referring the patients and their FNA samples to radiologists and pathologists with more experience in thyroid cancer. Moreover, we suggest that the decision to perform surgery should be made upon not only the thyroid FNA result, but the holistic clinical features of the patient.

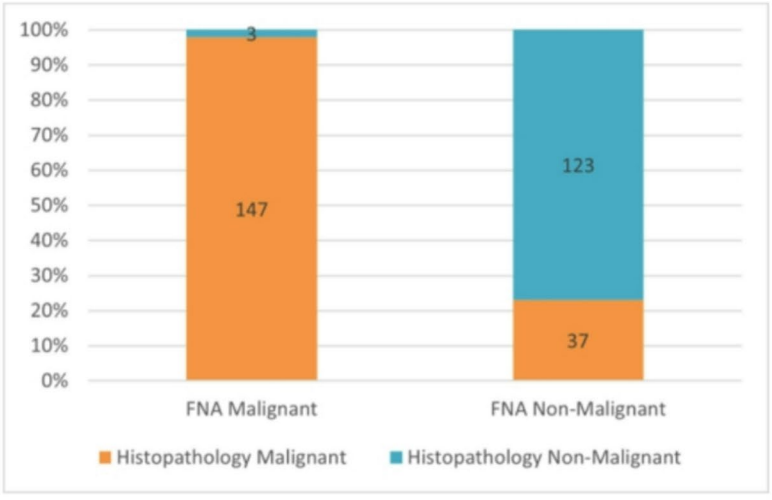
The size of the thyroid nodule is an easily defined feature by ultrasonography of the thyroid. In our study, the largest diameter (as the size) of the thyroid nodule was inversely correlated with the malignancy. All the cases were indicated for thyroid FNA based on the patients' clinical features, including their nodule size. Malignancy was observed in nodules with 1–3 centimeters of

Overall (indeterminate FNA cases excluded)



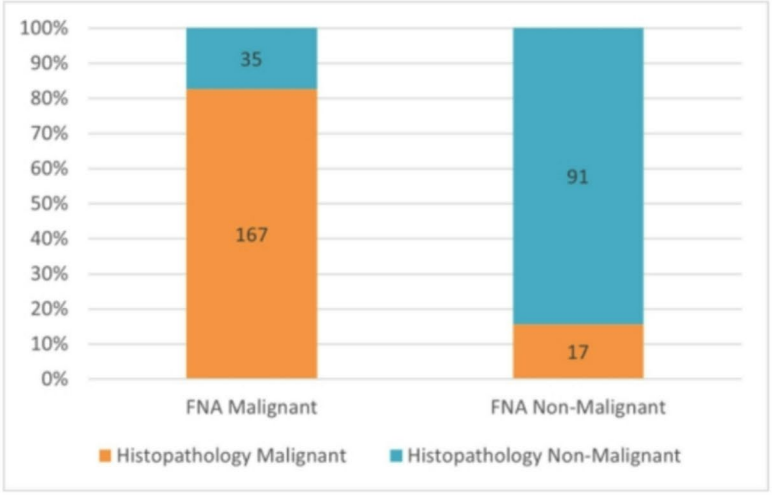
Accuracy	92%
Sensitivity	90%
Specificity	97%
PPV	98%
NPV	84%
FPR	2%
FNR	16%

Indeterminate FNA cases as non-malignant



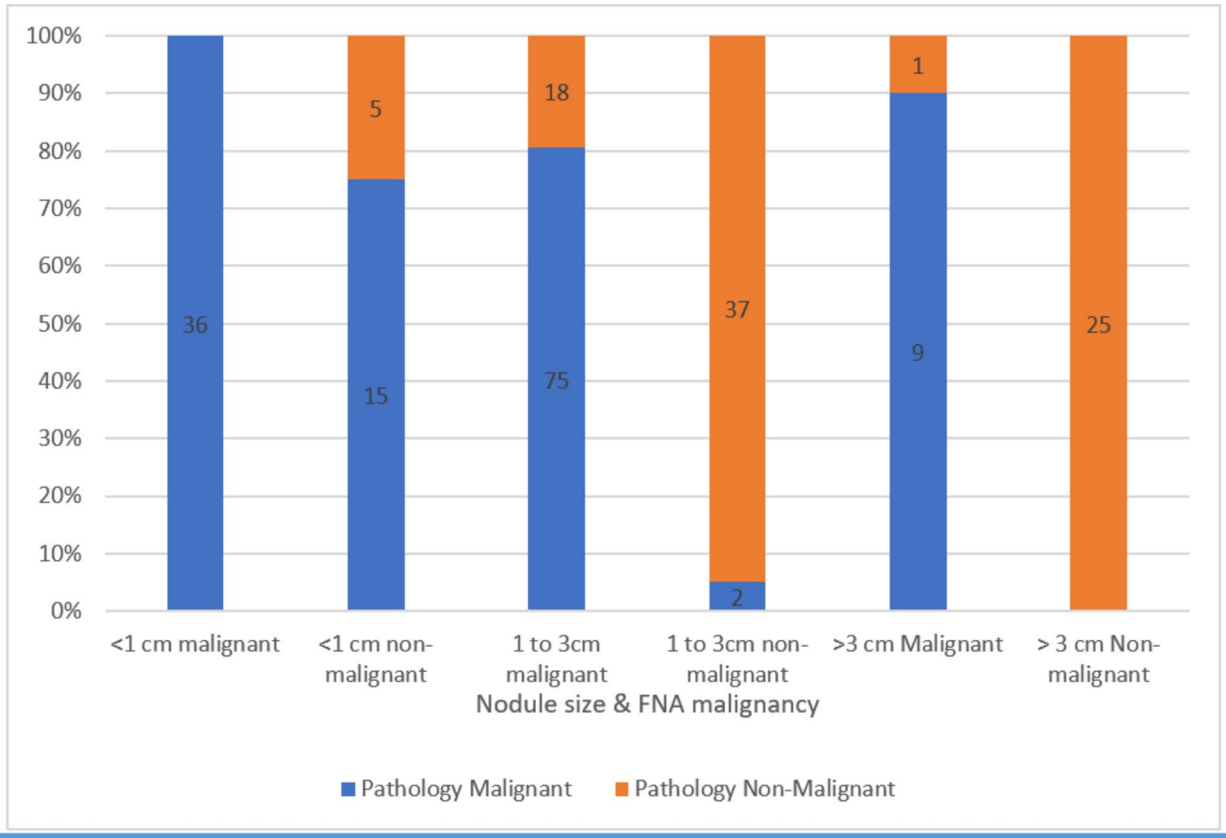
Accuracy	87%
Sensitivity	80%
Specificity	98%
PPV	98%
NPV	77%
FPR	2%
FNR	23%

Indeterminate FNA cases as malignant



Accuracy	83%
Sensitivity	91%
Specificity	72%
PPV	83%
NPV	84%
FPR	17%
FNR	16%

Fig. 2 Results of FNA in the diagnosis of malignancy in thyroidectomy patients and their corresponding detection measurements depending on inclusion of indeterminate cases as malignant or non-malignant (ratios are rounded up). FNA: fine needle aspiration, PPV: positive predictive value, NPV: negative predictive value, FPR: false positive rate, FNR: false negative rate



Size	Sensitivity	Specificity	Accuracy
< 1cm	70.6%	100%	73.2%
1 – 3	80.6%	94.9%	84.8%
> 3	90.0%	100%	97.1%

Fig. 3 A: Results of final pathology in different thyroid nodule size groups and the accuracy measures of thyroid FNA by including indeterminate cases in non-malignant group in different size groups. cm: centimeter

size in 70% of the cases ($n = 93/132$) and with less than one centimeter in 91% ($n = 51/56$). This inverse correlation was also shown by Cavello et al. in their analysis of 659 patients who underwent thyroidectomy [22]. In this study, the sensitivity and specificity of FNA improved in less than one centimeter group, to one to three centimeters group, to larger than three centimeters group. However, the rate of malignancy decreased from 91 to 70% to 28% in these groups as the size was increasing. Similar results were reported by Lind et al. in 1965 cases where FNA sensitivity for thyroid malignancy was 86.5% in nodules larger than one centimeter and 61.5% in nodules smaller than one centimeter [23]. These results suggest that in spite of the declining rate of malignancy in larger nodules, the accuracy of FNA increases. We recommend additional diagnosing techniques such as immunohistochemistry and genetic testing in nodules smaller than one centimeter in addition to cytologic evaluation of FNA samples.

The location of the nodules is another significantly correlated factor for malignancy, with the isthmus being the most observed location of malignant nodules, regardless of involvement of the right or left lobes. The same conclusion was reached by Jasim et al. in their analysis of 3241 nodules [24]. The sensitivity and specificity of thyroid FNA was higher in bilateral nodules and nodules in isthmus, however, the number of cases in our isthmus group was not sufficient for evaluating significance and the effect of location on thyroid FNA accuracy requires further investigation. We suggest that the patients with thyroid nodules in isthmus, unilateral nodules, and both isthmus and unilateral are better candidates for undergoing additional techniques for diagnosing thyroid cancer as suggested in the previous paragraph, however, FNA can provide accurate results if reported positive.

For the past few decades, different novel methods were introduced to improve the diagnosis accuracy of thyroid cancer. By analyzing the molecular changes in thyroid

cells via ThyroSeq v3 or different biomarker depositions in thyroid tissue using fluorescent immunohistochemistry or mass spectrometry imaging, the sensitivity of thyroid malignancy in indeterminate cases can increase up to 98% and prevent unnecessary diagnostic surgeries [25–27].

Among the limitations of our study was the inclusion of only two referral centers. However, these centers were the main referral centers for thyroid cancer and consisted of many patients from other provinces from Southern Iran. To ensures diversity among patients, further research in different populations is needed to challenge the results of our study. The small sample size and the very few significant variables based on logistic regression limited our capability to design a nomogram, and we recommend further evaluation on larger populations. Another limitation of our study was the absence of the patient's laboratory data to evaluate their effect on thyroid malignancy. Furthermore, our data was limited by selection bias and our results are only applicable to thyroidectomy surgery candidate cases.

Conclusion

FNA has proven to be a relatively suitable diagnostic tool for detecting malignant nodules, though it comes with specific limitations. Our study demonstrated that the overall accuracy of FNA in diagnosing malignancy was 92.2%, with a PPV of 98.0%, an NPV of 84.2%, a specificity of 96.8%, and a sensitivity of 89.6%. The diagnostic capability can vary based on the therapeutic approach to indeterminate thyroid FNA results. Sensitivity, specificity, and accuracy of FNA can be as high as 80%, 98%, and 87%, respectively, when considering indeterminate cases as non-malignant. The size of the nodule and the BSRTC classification of the nodule have a direct correlation with the accuracy of FNA in detecting the malignancy of the nodule. The accuracy of thyroid FNA increases with larger nodule sizes. We recommend using additional diagnostic methods (e.g. Molecular and genetic tests) for nodules with a higher risk of malignancy or lower FNA accuracy, such as nodules in the thyroid isthmus or those smaller than one centimeter.

Abbreviations

ROM	Risk of malignancy
FNA	Fine needle aspiration
BSRTC	Bethesda system for reporting thyroid cytopathology
TP	True positive
FP	False positive
TN	True negative
FN	False negative
PPV	Positive predictive value
NPV	Negative predictive value
FPR	False positive rate
FNR	False negative rate
PTC	Papillary thyroid carcinoma
MNG	Multinodular goiter
AUS	Atypia of undetermined significance

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None to declare.

Author contributions

RS conceived and designed the study. PM and SM performed the surgeries. SK collected the data. MMF wrote the first draft of the manuscript and analyzed the data. RS proofread the manuscript. All authors read and approved the final version before submission.

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None.

Data availability

SPSS data of the participant can be requested from the authors. Please write to the corresponding author if you are interested in such data.

Declarations

Ethics approval and consent to participate

The ethics committee of Shiraz University of Medical Sciences approved this study (IR.SUMS.MED.REC.1400.349). Patients' information was de-identified before data analysis and confidentiality of patient information was guaranteed and protected. Based on the retrospective nature of our study, written informed consent was waived by the Ethics committee of Shiraz University of Medical Sciences, and their information was obtained from their hospital records. Permission to carry out the study and access patient records was sought from the Shiraz University of Medical Science administrators, and the study was conducted in compliance in accordance with the relevant guidelines and regulations and the Declaration of Helsinki and was also approved by the ethics committee of the university. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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