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Full Length Research

Importance of fine needle aspirate in thyroid pathology in the Lebanese population- A retrospective analytical study of thyroid diseases from 2015 to 2017

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ABSTRACT: Thyroid cancer is the most common malignant endocrine tumor. Its clinical presentation is usually as a solitary thyroid nodule of increasing goiter size. As for diagnosis, ultrasound-guided thyroid Fine Needle Aspirate (FNA) followed by cytological examination is considered the standard practice due to its cost effective and minimally invasive nature. In this regard, FNA can be considered a screening test, selecting for surgery nodules with a greater probability of malignancy. The aim of the present study is to assess the importance of FNA in diagnosis of different thyroid pathologies in Lebanon. This study was retrospective in which data was collected by reviewing patients' medical files with thyroid pathology samples collected by FNA at the Institut National de Pathologie for the period of 2015-2017. The specificity and sensitivity of cytological diagnoses were evaluated based on histological diagnosis. The results show that a total of 735 FNA cytology were performed in 735 patients, of whom 165 (22.4%) were males and 570 (77.6%) were females. Mean age of the patients was 48.6±13.4 years. Amongst the 735 cases, 57 cases (7.8%) were classified as unsatisfactory, 526 cases (71.6%) as benign, 32 cases (4.4%) as follicular lesion of undetermined significance, 35 cases (4.8%) as suspicious for malignancy, 41 cases (5.6%) as suspicious for follicular neoplasm, and 44 cases (6.0%) as malignant. The mean size of nodule (19.4±10.2 mm) decreased by year from 22.3 mm in 2015 till 18.4 mm in 2017 ($p< 0.001$) and malignancy was higher with larger nodules ($p< 0.001$). Therefore, the sensitivity, specificity, positive predictive value, and negative predictive value were 85.7, 99.6, 75.0, and 99.8%, respectively. In conclusion, this study highlighted the relevance of FNA in diagnosing thyroid pathologies and evaluated malignancy prevalence. More studies are needed to test whether FNA's role is important in diagnosing thyroid nodules and ruling out malignancy.

Keywords: Follicular lesion, Fine Needle Aspirate, malignancy, neoplasm, thyroid pathology.

Abbreviations: AUS: Atypia of undetermined significance; **FLUS:** Follicular Lesion of Undetermined Significance; FN: Follicular Neoplasm; **FNA:** Fine-Needle Aspirate; **FNAC:** Fine Needle Aspirate Cytology; **INP:** Institut National de Pathologie; **NPV:** Negative Predictive Value; **PPV:** Positive Predictive Value; **TBSRTC:** The Bethesda System for Reporting Thyroid Cytopathology; **SETTLE:** Spindle Epithelial Tumor with Thymus-Like Differentiation; **SFM:** Suspicious for Follicular Malignancy; **SFN:** Suspicious for Follicular Neoplasm; **US:** Ultrasonography.

INTRODUCTION

Thyroid pathologies are amongst the most common causes of diseases in the world. The most frequent thyroid disease in the community is a simple (diffuse) physiological goiter and that could be majorly due to the fact that one-third of the world's population is living in areas of iodine deficiency (Maniakas et al., 2018). Thyroid cancer, although rare, is the most common malignant endocrine tumor and accounts for 90% of the cancers of

the endocrine glands. Its clinical presentation is usually as a solitary thyroid nodule or increasing goiter size (Perros et al., 2014). Furthermore, concerning diagnosis, ultrasound-guided thyroid Fine Needle Aspirate (FNA) followed by cytological examination is considered the standard practice due to its cost effective and minimally invasive nature. FNA results' interpretation, thus, becomes the key step for clinicians to advise if more invasive evaluation is necessary (Cibas et al., 2017).

In an overview, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has established a uniform, tiered reporting system of diagnostic terminology and for thyroid FNA specimens. Using the TBSRTC, the cytopathologists can communicate thyroid FNA interpretation and report to the physician in terms that are succinct, unambiguous, and clinically useful (Baloch et al., 2020). Since the widespread acceptance of TBSRTC in clinical practice, questions have arisen over the proper use of the diagnostic categories, the recommended management (e.g., repeat FNA vs. surgery), and the implied risks of malignancy (Trimboli et al., 2020). However, FNA can be considered a screening test, selecting for surgery those nodules with a greater probability of malignancy and excluding benign pathologies from undergoing unindicted thyroidectomies or lobectomies (Vanderlaan et al., 2014).

Few studies have been conducted regarding thyroid pathologies in Lebanon. A recent one reported the prevalence of thyroid cancer in Lebanon between 2006 and 2016 (Saad et al., 2019). Another study presented the radiological characteristics and cytological findings of thyroid nodules undergoing FNA, as well as, potential predictors of inadequacy of this technique (Boutros et al., 2017). In addition, an epidemiological monocentric research described sociodemographic characteristics of thyroidectomies and related macroscopic findings to histological results (Abboud et al., 2015). Finally, a study was conducted regarding thyroid cancer in children (Dardas et al., 2009). Thus, it is of great need to report the prevalence of thyroid nodular diseases and establish correlations between demographic data and this pathology in Lebanon. Therefore, the aim of the present study is to assess the importance of FNA in diagnosis of different thyroid pathologies.

METHODOLOGY

Study design and population

A retrospective multicentric study was conducted over 735 patients having single or multiple thyroid nodules. Participants included in this study were males and females and having satisfactory thyroid samples. Patients having synchronous neoplasm of any kind except those diagnosed "in situation" as primary and not metastatic, as well as patients with missing demographic data or with unknown nodule were excluded from this study.

Data collection

Thyroid FNA samples were provided to the Institut National de Pathologie (INP) by several clinics and hospitals across Lebanon. The cytological diagnosis was based on the evaluation of FNAC smears. The latter were classified in accordance with the diagnostic categories (DC) implemented by the TBSRTC: DC I: Non-diagnostic, DC II: Benign, DC III: Atypia/follicular lesion of undetermined significance (AUS/FLUS), DC IV: Follicular neoplasm/suspicion of follicular neoplasm (FN/SFN), DC V: Suspicious for malignancy (SFM), DC VI: Malignant (Cibas et al., 2017). Whereas, in case of thyroid surgery, corresponding histopathological study was established on collected thyroidectomy specimens which were categorized then into benign or malignant.

Subsequently, data was retrieved from patients' files available at the INP from January 1st 2015 until December 31st 2017 and assorted according to the year of admission into three groups (Group 1: 2015; Group 2: 2016; Group 3: 2017). The main information gathered was related to demographics, history of malignancy and co-morbidities (when available), size of the nodule, FNA sample type, histological diagnosis (when available) and final diagnosis (when available). Comparisons were done between cytological and histological diagnosis in addition to cytological and clinical diagnosis.

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics, version 22. Quantitative variables were presented as means and standard deviation. The association between two qualitative variables was tested using Chi-square test and Fisher's exact tests of significance. The means of quantitative variables were compared using one-way ANOVA. A p-value <0.05 was considered to be statistically significant. Moreover, diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Ethical considerations

Access letters to patient archives were requested and sent to respective hospitals, physicians, clinics, and institutes, a permission to collect data from the INP archives was obtained. ID numbers were assigned to individual patient files for confidentiality purposes.

RESULTS

Demographics

A total of 735 FNACs were performed in 735 patients, of

Table 1. Descriptive statistics of demographic characteristics between 2015 and 2017.

Parameters	Total (n=735)	2015(n=184)	2016(410)	2017(n=141)	p-value
Age (per year)					
Valid answers	735	184	410	141	
Mean ±SD	48.6±13.4	47.1±12.6	48.7±13.9	50.3±12.9	0.093
Median	48.0	47.5	48.0	49.0	
Min - Max	10 -88	14 -80	11 - 88	10 - 84	
Gender					
Male	165(22.4%)	46(25.0%)	86(21.0%)	33(23.4%)	0.529
Female	570(77.6%)	138(75.0%)	324(79.0%)	108(76.6%)	
Nationality					
Lebanese	707(96.2%)	181(98.4%)	389(94.9%)	137(97.2%)	
Syrian	2(0.3%)	0(0.0%)	2(0.5%)	0(0.0%)	0.053
Palestinian	6(0.8%)	1(0.5%)	2(0.5%)	3(2.1%)	
Others	20(2.7%)	2(1.1%)	17(4.1%)	1(0.7%)	

Table 2. Descriptive statistics of nodule size between 2015 and 2017.

Nodule size (in mm)	Total (n=735)	2015(n=184)	2016(410)	2017(n=141)	p-value
Valid answers	735	184	410	141	
Mean ±SD	19.4±10.2	22.3±11.6	18.4±9.8	18.4±8.2	<0.001*
Median	16.0	18.0	15.0	16.0	
Min - Max	1 -80	5 -70	1 – 80	5 - 80	

whom 165 (22.4%) were males and 570 (77.6%) were females. Mean age of the patients was 48.6±13.4 year and the majority (96.2%) was Lebanese (Table 1).

The mean thyroid nodule size was 19.4±10.2 mm with a diameter ranging from 1 to 80 mm. Furthermore, the nodule mean size was larger in 2015 (22.3 mm) than 2017 (18.4 mm) (p<0.001) (Table 2).

With advancing age, the prevalence of thyroid nodules increased. Thyroid nodular disease was more frequent between the age of 18 and 60 years old (81.2%). Patients less than 18 years had an average of 18.8 mm nodule size, whereas patients above 18, distributed in two age groups (between 18 and 60, above 60 years old), had a mean size of 19.4 mm which demonstrated a slight increase in nodule size with age without being statistically significant (p=0.990). Only in patients between 18 to 60 years, their nodules reached 80 mm. Moreover, compared to males, females had significantly smaller nodules (18.8±9.5 mm vs. 21.3±12.0 mm, p=0.005).

Cytological findings

Of the 735 cases, 45 cases (6.1%) were classified as unsatisfactory, 559 cases (76.1%) as benign, 37 cases (5.0%) as follicular lesion of undetermined significance, 6 cases (0.8%) as suspicious for malignancy, 37 cases (5.0%) as suspicious for follicular neoplasm, and 51 cases (6.9%) as malignant.

Histological findings

Nodule size varies with histological diagnosis. Benign histology had smaller mean size than malignant histology but not statistically significant (18.3±9.1 mm vs. 25.4±17.7 mm, p=0.045) (Table 3). Moreover, when comparing histological diagnosis and age categories, no statistical significance (p=0.772) was found**.** Furthermore, a total of 5 malignant cases were aged between 18 to 60 years old and 2 malignant cases above 60. Majority of histological diagnosis between 18 and 60 years old was benign (98.6%)**.** And regarding patients less than 18 years, all cases were benign.

Concerning the correlation between histological and cytological diagnosis for 510 followed-up thyroid pathologies, 5 malignant cases on cytology were confirmed to be malignant by histology. A total of 501 benign cases on cytology were confirmed to be also benign on histology and only 1 benign case on cytology was found to be malignant on histology. In addition, out of 3 SFN cytology, 2 cases were confirmed benign by

Table 3. Descriptive statistics of nodule size by different histological results.

Nodule size (in mm)	Benign	Malignant	p-value
Valid answers	503	7	0.045
Mean ±SD	18.3±9.1	25.4±17.7	
Median	16.0	18.5	
Min - Max	2 - 80	5 - 55	

Table 4. Correlation between histological and cytological diagnosis.

Cytological diagnosis	Histological diagnosis	
	Benign	Malignant
ND[1]	0	0
Benign	501	1
FLUS[2]	0	0
SFN[3]	2	1
SFM[4]	0	0
Malignant	0	5

ND[1]: Non diagnostic, FLUS[2]: Follicular lesion of undetermined significance, SFN[3]: Suspicious for follicular neoplasia, SFM[4]: Suspicious for malignancy.

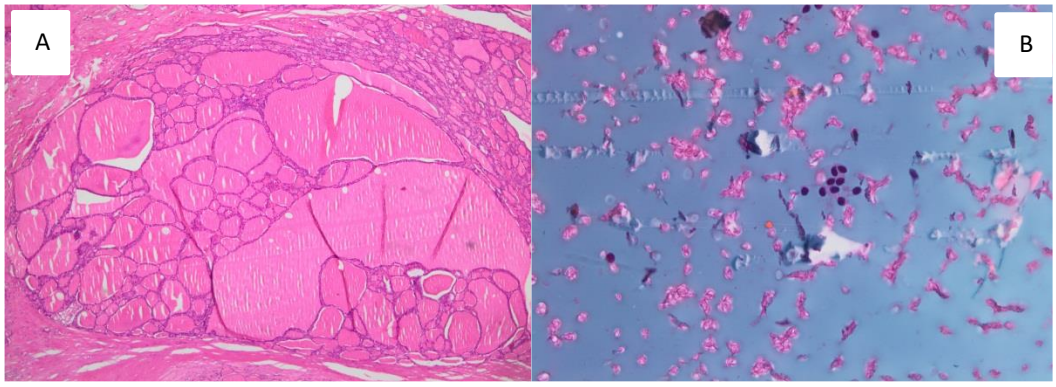

Figure 1. Benign thyroid nodule. A (x40) histology and B (x400) cytology.

histology and only 1 was malignant. These findings were statistically significant (p<0.001) (Table 4).

Clinical diagnosis

Out of 510 patients, a total of 7 different clinical diagnoses were obtained with benign follicular nodule being the most frequent one (98%, p<0.001) (Figure 1), papillary carcinoma constitutes 0.6% (Figure 2), follicular functional adenoma formed 0.4%, Hurthle cell carcinoma accounted for 0.4% of all cases (Figure 3). Per contrast, the other diagnoses (diffuse malignant lymphoma, hyperplastic non neoplastic thyroid parenchyma, SETTLE) were only present each in 0.2% of patients.

When comparing cytological and clinical diagnosis, there were significant differences in benign, SFN, and malignant cytological categories, as well as, benign follicular nodule clinical category (p<0.001)

Diagnostic accuracy of FNA

Based on histological examination as Gold standard, the diagnostic accuracy of FNA was calculated. Furthermore, unsatisfactory samples were excluded. The benign FNAC was considered a true negative if histopathological diagnosis was benign and false negative in case proven malignant on histology. Follicular lesion of undetermined significance (FLUS), suspicious for follicular neoplasms (SFN), suspicious for malignancy (SFM), and malignant cases were considered as true positive in cases where

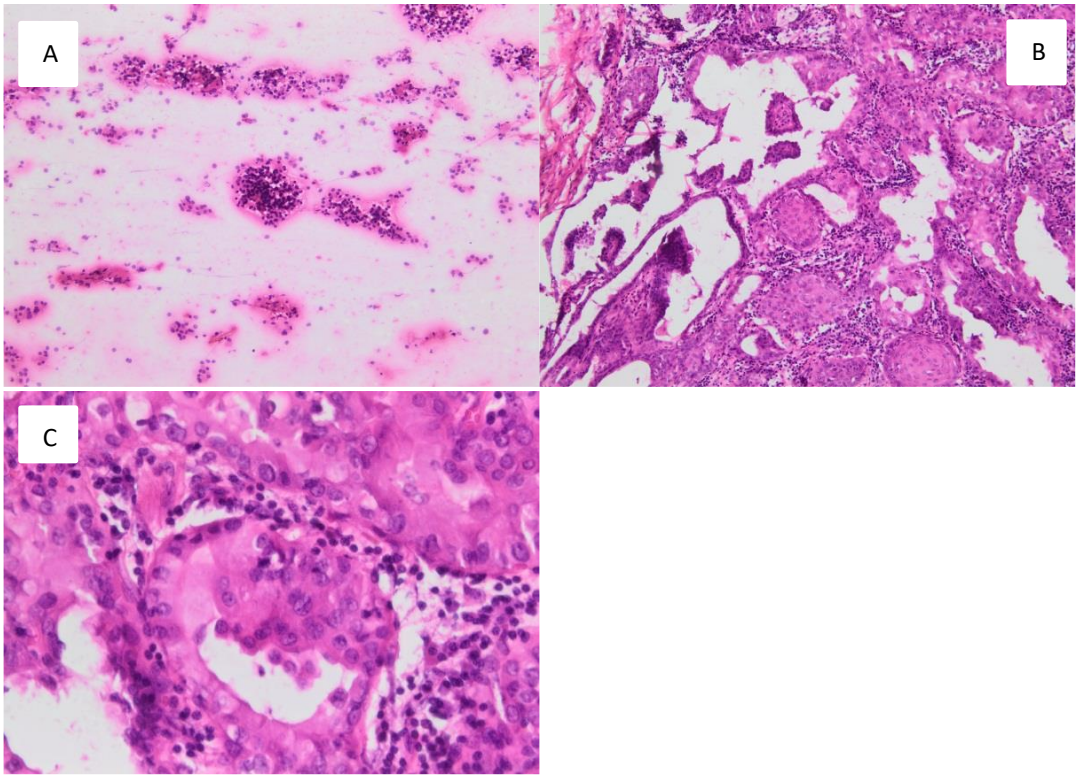

Figure 2. Papillary thyroid carcinoma: A (x100) cytology; B (x100) and C (x400) histology.

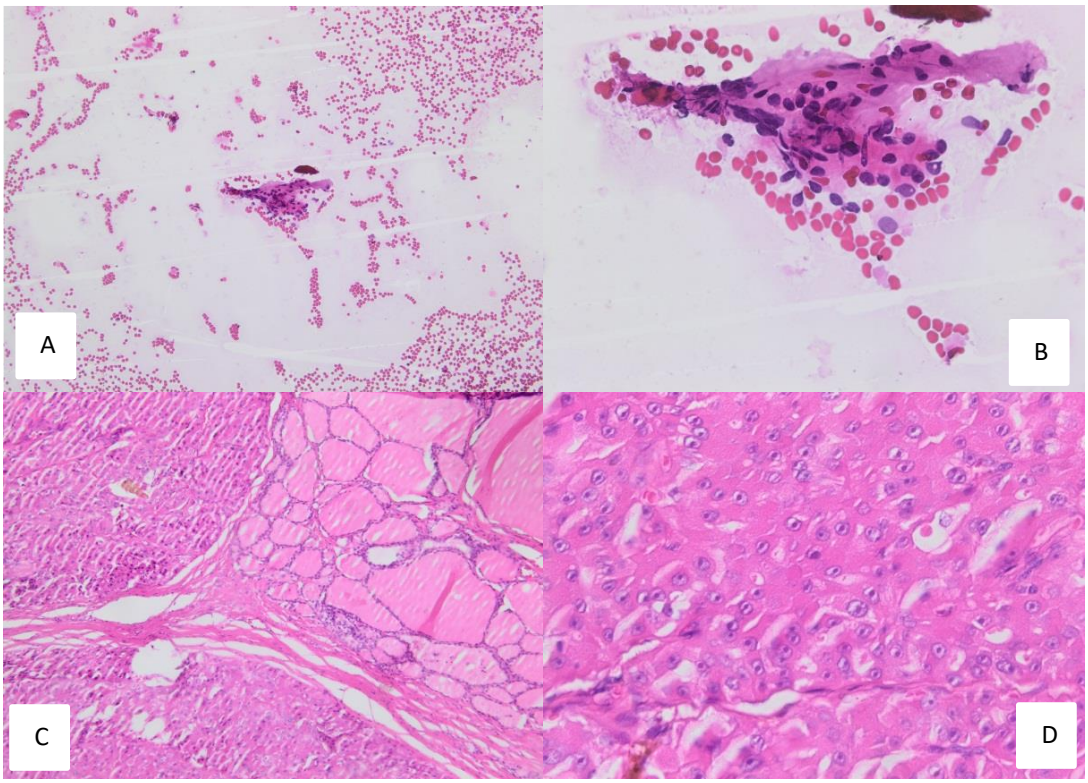

Figure 3. Thyroid FNA, cytology suspicious for Hurthle cell carcinoma: A (x100) and B (x400). Hurthle cell carcinoma, post-surgical diagnosis: C(x100) and D (x400).

Table 5. Diagnostic accuracy of FNA.

Parameters		Clinical diagnosis							
		Total		2015		2016		2017	
		SFN[1]/ Malignant	Benign	SFN/ Malignant	Benign	SFN/ Malignant	Benign	SFN/ Malignant	Benign
Cytological diagnosis	FLUS/SFN/SFM or Malignant	TP=6	FP=2	TP=4	FP=1	TP=0	FP=1	TP=2	FP=0
	Benign	FN=1	TN=501	FN=1	TN=104	FN=0	TN=313	FN=0	TN=84
Sensitivity (%)		85.7%		80.0%		N/A		100%	
Specificity (%)		99.6%		99.0%		99.7%		100%	
Positive predictive value (NPV)		75.0%		80.0%		N/A		100%	
Negative predictive value (NPV)		99.8%		99.0%		100%		100%	

SFN[1]: Suspicious for follicular neoplasia.

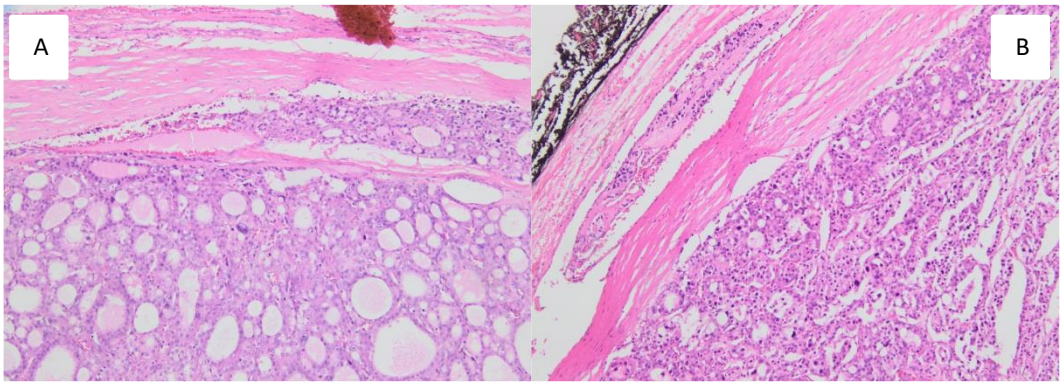

Figure 4. Follicular carcinoma, histology. A showing capsular invasion, B vascular invasion.

histological diagnosis revealed malignancy and considered false positive when no malignancy was found. Hence, the sensitivity of thyroid FNA was 85.7%, specificity was 99.6%, positive predictive value (PPV) was 75.0%, and negative predictive value (NPV) was 99.8% (Table 5).

Overall predicted malignancy

The overall predicted malignancy between January 2015 and December 2017 was 68.1% for Papillary carcinoma, while it was at a lower rate of 13.8% for Hurthle cell carcinoma, 7.4% for Follicular carcinoma (Figure 4), 5.3% for Anaplastic carcinoma, 2.1% for Medullary carcinoma as well as Thyroid lymphoma, and only 1.1% for Spindle epithelial tumor with thymus-like differentiation – SETTLE (Figure 5).

DISCUSSION

FNAC is a simple, minimally invasive, and cost-effective tool for the initial diagnosis of thyroid nodules. It can be considered a screening test, selecting for surgery nodules with a greater probability of malignancy. Hence, FNA should be accurate in distinguishing benign from malignant thyroid lesion (Cibas et al., 2017).

The age of patients at the time of presentation in this studies was 48±13.6 years, and many studies in Lebanon and other countries showed similar age (Bhatti et al., 2010; Saad et al., 2019). However, other research by Kenny Robert et al. (2016) showed younger sample of patients. This might suggest that the age of presentation might be affected by geographical areas that have different iodine status as well as the mean of screening, examination, and imaging method (X-ray, laryngoscopy, US) used.

Furthermore, regarding the relationship between the histological diagnosis and age of patients, the results were conflicting. Some studies showed no correlation between these 2 parameters which is in agreement with the findings in this study (Kenny Robert et al., 2016). However, other studies identified a direct (El-Gammal et al., 2019) or indirect (Kwong et al., 2015) relationship between age and histological diagnosis. This might be due to the uniform

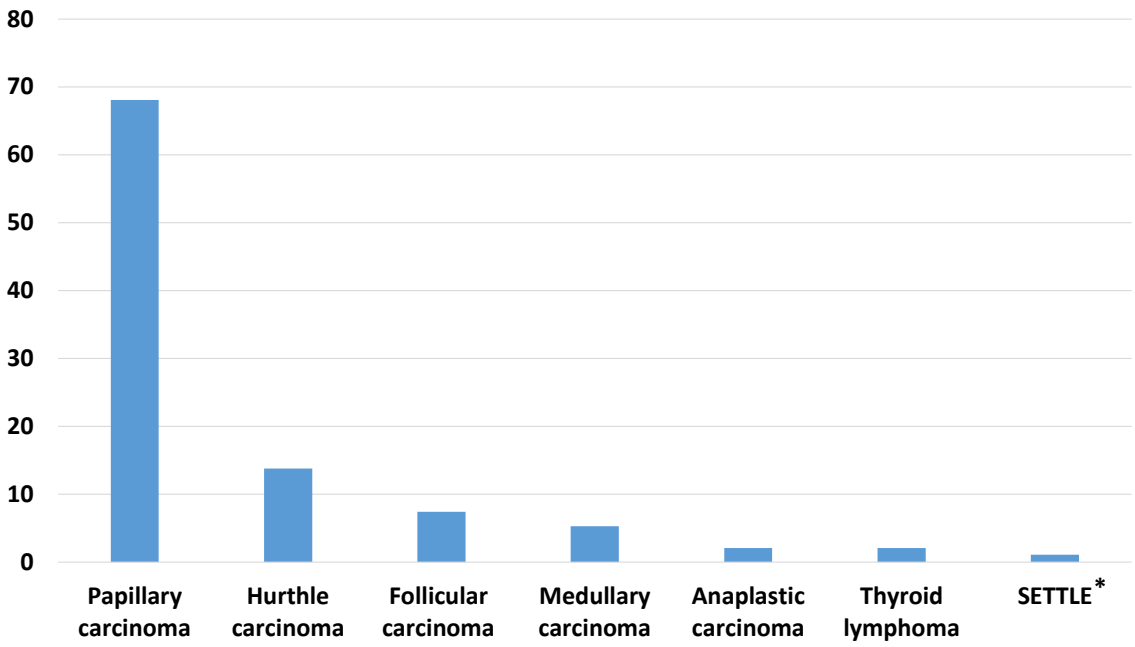

Figure 5. Overall (%) predicted malignancy between January 2015 and December 2017.
*SETTLE: Spindle Epithelial Tumor with Thymus-Like Differentiation.

interpretation of thyroid nodule histology by the same group of thyroid pathologists in some studies or the very low malignancy findings in other studies.

Moreover, concerning the correlation between nodule size and the rate of malignancies, some findings (Mohamed et al., 2019; Jinih et al., 2020) are in agreement with this study. This proved that there is no relationship between these 2 parameters, whereas others showed a direct relationship between nodule size and malignancy rate (El-Gammal et al., 2019). This difference in results can be explained by the fact that large nodules are prone to false negative results and small nodules are less likely to undergo surgeries.

Regarding recent studies done in the MENA region, a 10 year-retrospective study of 928 patients conducted by Saad et al. (2019) in Lebanon, had a total of 298 FNA performed, whereas in this study, 735 FNA were achieved. Unlike the objective of this study that focused on assessing the importance of FNA in the diagnosis of different thyroid pathologies, their work aimed to determine the prevalence of thyroid cancer in Lebanon between 2006 and 2016. Similar to the results of this study, their study identified that papillary carcinoma was the most common finding with an incidence of 91.45% (vs. 68.1% in the current study). However, their results showed no Hurtle carcinoma and SETTLE in their population, whereas in this study, both cancers' frequencies reached 13.8% and 1.1%, respectively. Besides, according to their study, tumor size usually was less than 1 cm whereas the mean size of malignant nodule in this work was 24.7 mm.

In addition, based on experience from an academic tertiary care center in Lebanon, Boutros et al. (2017) reported that most thyroid nodules were located either in the right or left lobe and less likely in the isthmus. The majority of the nodules undergoing FNA were benign (76.7%) as also shown in this study (71.6%). This later finding underlines the importance of using FNA as a screening tool prior to surgery to avoid unnecessary thyroidectomies or lobectomies.

In a Lebanese case series done by Tabbara and Aftimos (1979), only 12% of thyroid patients were male and age ranged from 3 to 85 years. They also found that uninodular goiter was the most common diagnosis. Frequency of cancer reached 4.3% with follicular carcinoma being the most abundant type unlike this study finding. This study also proved that histological diagnosis presents with many difficulties and problems regarding some lesion features such as true capsular and vascular invasion, true papillary structures and true malignant cyto-nuclear characteristics. Researchers proposed a meticulous histological diagnosis as well as a good macroscopic and microscopic evaluation to overcome this limitation.

Moreover, Taha et al. (2020) conducted a 16 year-retrospective study of 1174 Qatari patients where they demonstrated a higher sensitivity for US-guided thyroid FNA than palpation guided FNA. Both approaches revealed a higher post-operative malignancy in benign and unsatisfactory thyroid nodule than the predicted risk in Bethesda. This finding is also in accordance with results of a Turkish study (Badak et al., 2020).

The current literature reported variable findings regarding cytological diagnosis according to Bethesda,

Table 6. Comparison of similar articles and their results.

Parameters	This study	Zhu et al., 2020	Muhammad et al., 2020	Erkinuresin et al., 2019	Ajitha et al., 2019	Georgescu et al., 2017
Total number of FNA	735	2781	100	149	1175	319
Cytological diagnosis						
Benign	76.10%	17.10%	82%	55.70%	83.30%	69.30%
FLUS[1]	5.00%	15.80%	-	9.40%	2.00%	15.20%
SFN[2]	5.00%	2.30%	-	8.72%	1.40%	-
SFM[3]	0.80%	11.60%	-	6.04%	1.90%	1.30%
Malignant	6.90%	38.50%	18%	10.74%	1.80%	0.30%
ND[4]	6.10%	14.80%	-	9.40%	9.60%	13.90%
Histological correlation	510	1122	80	149	132	49
Benign	98.60%	11.80%	90.00%	-	86.36%	30.61%
Malignant	1.40%	86.40%	10.00%	-	13.63%	26.53%
Other	0.00%	1.80%	-	-	-	42.86%
Diagnosis						
Benign follicular nodule	98.00%	11.70%	-	2.68%	-	64.55%
Papillary carcinoma	0.58%	84.49%	5.00%	11.41%	12.87%	1.58%
Other diagnosis	0.20%	3.81%	-	85.91%	-	33.87%
Diagnostic values						
Sensitivity	85.70%	98.00%	80.00%	57.89%	64.7%	76.47%
Specificity	99.60%	84.00%	98.39%	88.10%	97.1%	83.10%
Positive predictive value	75.00%	99.40%	80.00%	52.38%	78.5%	35.10%
Negative predictive value	99.80%	58.30%	98.39%	90.24%	94.4%	96.70%

[1]FLUS: Follicular lesion of undetermined significance, [2]SFN: Suspicious for follicular neoplasia, [3]SFM: Suspicious for malignancy, [4]ND: Non diagnostic.

clinical diagnosis and diagnostic accuracy values in thyroid nodules FNAs (Zhu et al., 2020; Muhammad et al., 2020; Erkinuresin et al.,2020; Ajitha et al.,2019; Georgescu et al., 2017) (Table 6).

In this first of its kind study that tackles the diagnostic accuracy of FNA, samples were receive all over the country which rendered this study statistically representative. However, this study has some limitations. Since only thyroid disease patients were included, the data was not suitable to estimate the prevalence of thyroid pathology in Lebanon. Furthermore, follow-up data and final diagnosis were missing in a large number of patients' files which affected the finals findings. As a result also, ultrasonographic, clinical and cytological predictors of malignancy among indeterminate categories (FLUS, SFN, and SFM) could not be investigated.

Conclusion

While misdiagnosing a patient implies unnecessary surgeries and influences the overall quality of life of patients with thyroid pathologies, and knowing that FNAC report highly influences thyroidectomy decision, it can be concluded that the diagnostic accuracy of FNA in Lebanon is very satisfactory. However, more retrospective and prospective studies will still be needed to test whether FNA's role in diagnosing thyroid nodules and ruling out malignancy will be of importance. In addition, further research is warranted to identify ultrasonographic, clinical and cytological thyroid features that could predict malignancy in cytological suspicious thyroid nodules. Finally, the prevalence of thyroid disease is high and widespread in the Lebanese community, therefore, higher interest must be expressed in future studies in identifying causes, as well as establishing a proper diagnostic and therapeutic approach to thyroid nodules.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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