Fine-Needle Thyroid Aspiration Biopsy: Clinical Experience at the Endocrinology Clinics of the University Hospital of Puerto Rico

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Objective: This study aimed to establish a profile of the ultrasound-guided thyroid fine-needle aspiration biopsies (FNABs) performed at the endocrinology clinics of the University Hospital of Puerto Rico.

Methods: A retrospective study was conducted to assess all the thyroid FNABs performed from July 1, 2011, to December 31, 2013. Data on socio-demographic, FNAB cytology, surgery, and histopathology were collected from medical records. A chi-square test was used to assess associations between predictors and outcome. McNemar's test was used to compare FNAB cytology and histopathology results.

Results: A total of 240 FNABs were performed on 192 patients; 91.2% were female. The distribution of the cytological diagnoses was as follows: 181 (75.4%) were benign; 39 (16.3%) were non-diagnostic; 15 (6.3%) were indeterminate; and 5 (2.1%) were malignant. A malignant cytology was more likely in patients younger than 45 y/o than in their older counterparts (p = 0.01); a similar result was found for patients who smoked vs. those who did not (p = 0.02). Benign nodules were more likely to be larger than 1 cm than were those that were malignant (88.2% vs. 25%). Histopathology results were available for 38 nodules; there were no statistically significant differences between the cytology and histopathology results (p>0.05). The sensitivity and specificity for FNAB cytology were 75% and 100%, respectively. Of the nodules with an initial indeterminate cytology (47%), 71% demonstrated, ultimately, benign histopathology.

Conclusion: In our study, most of the FNABs performed yielded a benign cytology. A high concordance was shown between cytology and histology. For those with indeterminate cytology, the majority of cases demonstrated benign histopathology. These data suggest the need to implement other approaches, such as the development and subsequent use of molecular markers, to improve our diagnostic and therapeutic strategies, this according to our population-based disease prevalence. [*P R Health Sci J 2017;36:5-10*]

Key words: Thyroid fine-needle aspiration biopsy, Cytology, Thyroid nodules

Thyroid nodules constitute a very common clinical finding, with an estimated prevalence of 4 to 7% in the United States' general population (1). Most of these thyroid nodules first come to clinical notice after being found by the patient, an incidental finding during physical examination or after an imaging study. Their significance rests in excluding thyroid cancer, as the differential diagnosis is broad and ranges from benign to malignant disorders (2). Although most thyroid nodules are benign hyperplastic lesions, past research has determined that thyroid cancer occurs in 5 to 15% of thyroid nodules (after adjusting for age, sex, radiation exposure, and family history). Differentiated thyroid cancer (DTC)—papillary and follicular thyroid cancers—account for up to 90% of all cases (3). The risk of malignancy for non-palpable nodules is the same as for palpable nodules of corresponding size (4). In 2009, the American Thyroid Association guidelines for the management

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of thyroid nodules and DTC advised that upon the detection of a thyroid nodule, every patient should undergo a complete history and physical examination focusing on the thyroid gland, measurement of serum thyroid stimulating hormone (TSH) with radionuclide scan if the value is below normal, and thyroid ultrasound to assess sonographic features, as well to determine the presence of additional nodules and lymphadenopathy, with the subsequent performance of a fine-needle aspiration biopsy (FNAB), as indicated (3).

Fine-needle aspiration is an easy, safe, and precise procedure used for the study of tissue samples for cytologic examination (5). It is currently the procedure of choice for the evaluation of thyroid nodules and aids in the stratification of those patients in need of further management, recommending that those patients with cytologic examinations suggestive of cancer undergo surgery. According to the current literature, the overall accuracy of FNAB is over 95% (6,7). Moreover it is recommended that, when available, FNAB should be guided by sonography, as it has shown in retrospective studies to lower the rate of false-negative results and thus improve global diagnostic accuracy (8).

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) established 6 general diagnostic categories for describing thyroid FNAB results, with each category implying a particular cancer risk and linking said risk to a rational clinical management. These categories include non-diagnostic, benign, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), follicular neoplasm or suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy, and malignant (9). A cytology result suggestive of primary thyroid malignancy would undoubtedly prompt surgical intervention, while the management of those nodules categorized as AUS/FLUS, FN, or suspicious for malignancy—also termed indeterminate cytology—is more variable and might include repeat FNAB, molecular testing, close surveillance, or diagnostic surgery. A repeated FNAB is usually indicated in non-diagnostic specimens (3,10). Surgical resection for benign nodules might be indicated for symptomatic thyroid masses or goiters (11).

In recent years, several studies have compared the correlation of thyroid nodule cytology results with the corresponding final histopathology, and, still, false-positive and false-negative results present a challenge (12). In a recently published article of thyroid cytology, a second review of 3885 specimens resulted in a changed BSRTC classification in 32% of cases, which definitely leads to alterations in both clinical and surgical management (13). Routine second-opinion review of indeterminate thyroid FNAB was reported to potentially obviate the need for diagnostic thyroidectomy in 25% of the cases in 1 series (14). Moreover, testing for molecular markers has been evolving as an additional tool for improving diagnostic accuracy with regard to these nodules, although long-term outcome data on the use of these markers to guide therapeutic decision-making in patients with thyroid nodules are missing. It is well known that the prevalence of malignancy within the population being tested influences the negative and positive predictive values of these tests (10,15).

Ramírez et al. described a significant increase in the incidence of thyroid cancer in Puerto Rico (P.R.) for the year 2004 (as compared to the previous 20 years); this change was mostly due to an increase in papillary thyroid carcinomas (16). This increase is linked to a rising concern regarding thyroid cancer and, subsequently, the taking of a more aggressive approach toward thyroid nodules, when found. This study aimed to establish a profile of the ultrasound-guided thyroid fine-needle aspiration biopsies performed at the endocrinology clinics of the University Hospital of P.R. and describe the most common cytological diagnosis, patient risk factors, sonographic characteristics of the nodules, and histopathological results.

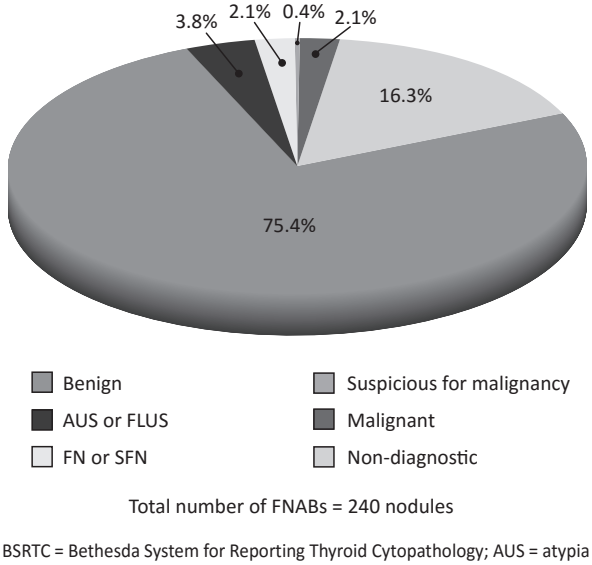
Methods

The present study is a retrospective analysis of pre-existing information on adult (≥ 18 years old) patients who underwent thyroid FNAB procedures at the endocrinology clinics of the University Hospital of P.R. from July 1, 2011, through December 31, 2013 (n = 192). We excluded patients with FNABs performed on non-thyroidal tissue including lymph nodes and those whose procedures were performed at outside centers. All data on socio-demographics, FNAB cytology, surgery, and histopathology were collected from medical records. Body mass index (BMI) was calculated as kg/m^2; individuals were categorized as being underweight ($<18.5 kg/m^2$), normal weight ($18.5–24.9 kg/m^2$), overweight ($25.0–29.9 kg/m^2$), or obese ($\geq 30 kg/m^2$). Tissue cytology for 240 nodules was recorded as non-diagnostic, benign, malignant, AUS/FLUS, FN/SFN, or suspicious for malignancy, according to BSRTC criteria; however, the main analysis was restricted to benign and malignant nodules. The study was approved by the University of Puerto Rico Medical Sciences Campus Institutional Review Board. All statistical analysis was performed using Stata software version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Descriptive analysis was conducted on the patient- and FNAB-level (i.e., including repeated FNABs). Chi-square, Fisher's exact, and Mann–Whitney tests, as appropriate, were conducted to assess associations between predictors (i.e., risk factors, sonographic characteristics) and outcome (i.e., FNAB cytology results). FNAB cytology and histopathology results were compared using sensitivity/specificity measures and McNemar's test; percent agreement and Cohen's kappa coefficient were also calculated. Statistical significance was determined as a p-value of less than 0.05.

Results

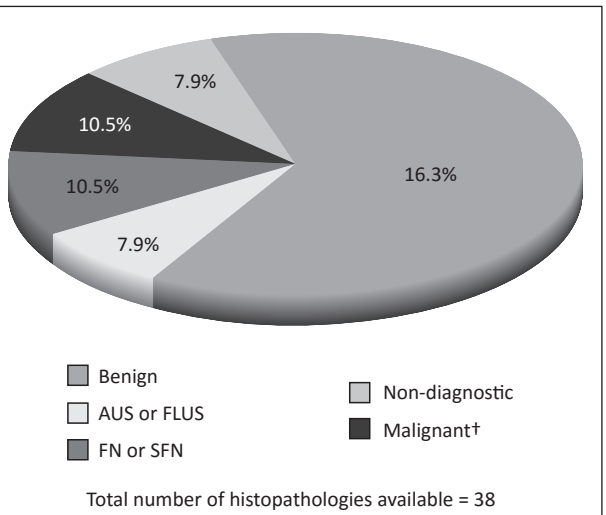
In our study, 91% of the cases were female and had a median age of 51 years (range: 19–83). A total of 240 nodules from the 192 patients underwent FNAB. Most of the FNABs (75.4%) were benign (Figure 1). All malignant cytology was due to papillary thyroid carcinomas. Histopathology results were

available for 38 nodules (Figure 2). Among the nodules with a corresponding initial indeterminate cytology, 7 out of 15 nodules (47%) underwent surgical resection; of these nodules, 8% had a final malignant histopathology. All the nodules with non-diagnostic cytology that underwent surgical resection were benign. Of those nodules with an initial benign FNAB, 1 nodule (4.2%) proved to be malignant, according to the final pathological result.



BSRTC = Bethesda System for Reporting Thyroid Cytopathology; AUS = atypia of undetermined significance; FLUS = follicular lesion of undetermined significance; FN or SFN = follicular neoplasm or suspicious for follicular neoplasm; FNABs = Fine needle aspiration biopsies. *Assessment was made per nodule

Figure 1. Distribution of Cytological results according to BSRTC*



AUS = atypia of undetermined significance; FLUS = follicular lesion of undetermined significance; FN or SFN = follicular neoplasm or suspicious for follicular neoplasm. †All nodules with Suspicious for malignancy/malignant cytologies were recommended surgery, but it was unknown if one of the nodules- in each of these categories had surgery.

Figure 2. Percent of surgeries performed at each cytological category

Patients with malignant cytology were more likely to be under 45 years old (100% vs. 33%; p = 0.01) and smokers (75% vs. 17.5%; p = 0.02) than were those with benign nodules. No significant association (p>0.05) was found between malignancy (as confirmed by FNAB cytology results) and family history of thyroid cancer, radiation exposure, BMI, or TSH level. Most patients with either benign or malignant cytology were biochemically euthyroid, with TSH levels within the established reference range (Table 1). Benign nodules were more likely to be larger than 1cm than were malignant ones (88.2% vs. 25%; p = 0.01), but no other sonographic characteristics showed associations with cytology results (Table 2).

There was no statistically significant difference between cytology and histopathology results (p>0.05) (Table 3). An agreement of 95.45% (k = 0.83; p<0.001) was found between FNAB cytology and histopathology results. Using histopathology as a gold standard for definitive diagnosis, the sensitivity and specificity of FNAB cytology were determined (75% and 100%, respectively).

Discussion

Thyroid nodules are one of the most common clinical problems encountered by endocrinologists worldwide. It is also well established that the prevalence of thyroid nodules depends on the population studied (10,17). According to the Surveillance, Epidemiology, and End Results Program (SEER), thyroid cancer represents 3.8% of all new cancer cases in the U.S. Moreover, for the year 2016, 64,300 new cases of thyroid cancer and 1,980 deaths from this disease were estimated (18). Thus, excluding thyroid malignancy, which has been reported in 5 to 15% of these nodules, remains critical (3).

In our study, most FNABs performed had a benign cytology, followed by non-diagnostic and indeterminate biopsies; fewer than 5% of our tissue samples demonstrated malignant cytology. Similar to what has been reported in other institutions, a higher-than-ideal proportion of non-diagnostic cytologies were present in our population (16.3% vs. <10%). This is most likely because of the lack of on-site determination of tissue adequacy, which was not routinely performed in our clinics during the study period, as is now advocated by most experts (9,19). All malignant cytologies were due to papillary carcinoma of the thyroid, which is not surprising as the reported increased incidence of thyroid carcinomas in the last decades has been largely due to a rise in the rate of papillary thyroid carcinomas. Puerto Rico has not been the exception with respect to this increasing trend, with a 2.3-fold increase in the incidence rate of thyroid cancer from the period of 1985 to 2004 (16).

A malignant cytology was associated with those patients younger than 45 years old, even though several studies have found higher rates of malignancy associated with extremes of age (20). Having a family history of thyroid malignancy did not seem to be predictive of a malignant cytology in our population; however, the number of family members affected

Table 1. Socio-demographics and risk factors, among all and by FNA cytology results of thyroid nodules

	FNA Cytology*			
	Overall (n=192) n (%)	**Benign (n=153) n (%)**	**Malignant (n=4) n (%)**	**P-value†**
Gender				
Male	17 (8.9)	11 (7.2)	1 (25.0)	0.28
Female	175 (91.2)	142 (92.8)	3 (75.0)	
Age (years)				
Mean ± SD	49.3 ± 14.0	49.3 ± 13.9	33.3 ± 9.4	0.02
Median (min, max)	51.0 (19, 83)	51.0 (19, 83)	36.5 (20, 40)	
Age categories (years)				
≥45	125 (65.1)	102 (66.7)	0 (0.0)	0.01
<45	67 (34.9)	51 (33.3)	4 (100.0)	
BMI (kg/m^2)				
Mean ± SD	29.7 ± 6.7	29.5 ± 6.9	33.3 ± 9.1	0.27
Median (min, max)	28.8 (17.3, 59.2)	28.6 (17.3, 59.2)	35.4 (21.0, 41.4)	
BMI categories (kg/m^2)				
Underweight (<18.5)	1 (0.5)	1 (0.7)	0 (0.0)	0.49
Normal (18.5-24.9)	52 (28.0)	42 (28.4)	1 (25.0)	
Overweight (25-29.9)	55 (29.6)	45 (30.4)	0 (0.0)	
Obese (≥30.0)	78 (41.9)	60 (40.5)	3 (75.0)	
Have you ever smoked?‡				
Yes	35 (19.3)	25 (17.5)	3 (75.0)	0.02
No	146 (80.7)	118 (82.5)	1 (25.0)	
Family history of Thyroid Cancer‡				
Yes	16 (8.9)	11 (7.6)	0 (0.0)	>0.99
No	164 (91.1)	133 (92.4)	3 (100.0)	
History of childhood irradiation to Head and Neck‡				
Yes	1 (0.6)	1 (0.7)	0 (0.0)	>0.99
No	175 (99.4)	140 (99.3)	4 (100.0)	
TSH levels (value, mIU/L)‡				
Suppressed (<0.45)	22 (11.6)	17 (11.3)	1 (25.0)	0.38
Normal (0.45-4.12)	131 (69.0)	104 (68.9)	2 (50.0)	
Elevated (>4.12)	37 (19.5)	30 (19.9)	1 (25.0)	
Medical history§				
Hypothyroidism	90 (46.9)	70 (85.4)	1 (50.0)	0.29
Hyperthyroidism	16 (8.3)	12 (14.6)	1 (50.0)	
Thyroid replacement therapy**				
Yes	89 (46.4)	68 (44.4)	1 (25.0)	0.63
No	103 (53.7)	85 (55.6)	3 (75.0)	
Anti-thyroid therapy††				
Yes	10 (5.2)	9 (5.9)	1 (25.0)	0.23
No	182 (94.8)	144 (94.1)	3 (75.0)	

*FNA cytology of 35 patients were not included due to non-diagnostic/unsatisfactory and/or indeterminate results; †Fisher Exact test or Mann-Whitney test were used, as appropriate, to compare characteristics between FNA cytology results; ‡Total may not equal the overall sample size ; §A total of 86 patients (44.8%) did not have a history of hyperthyroidism or hypothyroidism; **Thyroid replacement therapy includes Levothyroxine, Levoxyl, Synthroid, and Thyrosine complex; ††Anti-thyroid therapy includes Propylthiouracil and Methimazole.

was not taken into account. According to the literature, the probability that a given patient's thyroid malignancy is sporadic surpasses 60% only when 2 first degree members of that patient's family are affected by the disease; the familial component attains greater significance once the number of affected family members reaches 3 or more (10,21). Most of the patients who underwent thyroid FNAB were euthyroid, according to the last TSH available at the moment of the sampling, and in those with elevated TSH levels, the vast majority of the nodules were benign. It has been reported in previous studies that a higher TSH level correlates with an increased risk of malignancy, even when those levels are at the top of the normal reference range (22). It should be noted that TSH levels were not measured in the same laboratory by the same generation assay or at the same time of the biopsy but were gathered through record review. In our study, the typical high-risk sonographic characteristics (nodule size >1cm, solid, hypoechogenicity, irregular margins, microcalcifications, shape taller than wide, intranodal vascularity) were not associated with higher rates of malignant biopsies (3,23). This could be related to the inter-observer variability usually associated with the ultrasound technique, since the ultrasounds were mostly performed at outside institutions, and in many cases very limited information was available. Reports were not standardized nor were they compiled by the same personnel, which could definitely affect the interpretation of sonographic characteristics and patient risk stratification..

A high concordance was shown between cytology and histology results in our sample. Sensitivity and specificity were 75% and 100%, respectively. Seventy-one percent of indeterminate nodules demonstrated benign histopathology; nevertheless, fewer than 50% of these underwent resection. In order to better determine malignancy risk, physicians at individual institutions are being encouraged to make independent assessments based on each of the Bethesda cytology categories (10). One of the strengths of our study is that our endocrinology clinics receive referrals from physicians throughout the island of Puerto Rico, which allows our subject profiles and multiple variable analyses to be extrapolated to the island's population as a whole. Until now, limited information has been available regarding the most common thyroid nodule cytological diagnosis and whether the risk factors for malignancy reported in the literature have also been observed in our Puerto Rican population. Study limitations include the small sample size, especially for our cytology/histopathology comparison analysis, missing

Table 2. Distribution of ultrasonographic characteristics, among all and according to FNA cytology results* (n=157)

Ultrasonographic characteristics	Overall n (%)	No. of Benign (%)	No. of Malignant (%)	P-value†
Size > 1 cm	136 (86.6)	135 (88.2)	1 (25.0)	0.01
Hypoechoic	83 (52.9)	81 (52.9)	2 (50.0)	>0.99
Solid	19 (12.1)	17 (11.1)	2 (50.0)	0.07
Increased nodular vascularity	12 (7.6)	11 (7.2)	1 (25.0)	0.28
Irregular margins	13 (8.3)	13 (8.5)	0 (0.0)	>0.99
Micro-calcifications	18 (11.5)	17 (11.1)	1 (25.0)	0.39
Shape taller than wider in transverse dimension	1 (0.6)	1 (0.7)	0 (0.0)	>0.99

*FNA cytology of 35 patients were not included due to non-diagnostic/unsatisfactory and/or indeterminate results. †Fisher's Exact test was performed.

Table 3. Concordance between FNA cytology and surgical histopathology (N =22)

Surgical Histopathology	FNA cytology		P-value*
	Benign	Malignant	
Benign	18	0	>0.99
Malignant	1	3	

*McNemar's test was used to compare cytological and histopathological results.

data from patients who were sent for repeat FNABs after an initial indeterminate or non-diagnostic cytology, and patients who were lost to follow up, which could have led to a loss of statistical power.

In recent years, modalities of molecular testing have become available to aid in ruling out/in malignancy of indeterminate thyroid nodules, depending on the test used (15,24). Moreover, to help establish the clinical validity of these tests—including sensitivity, specificity, and predictive value—in distinguishing different group of patients, the prevalence of the disease in the population under study must be known (25). The data in our study suggest the need to establish other approaches in order to improve our diagnostic and therapeutic strategies, according to our population-based disease prevalence. Although molecular testing is not performed at our institution, this study provides initial data that support the need to incorporate molecular markers in our practice to predict those at lower risk for malignancy and, thereby, avoid unnecessary surgeries.

Conclusion

Thyroid nodules represent a very common reason for seeking an endocrinological evaluation. The growing incidence of differentiated thyroid cancer worldwide, as well as in our general practice, has led to a more aggressive approach to these nodules. Although a combination of history, laboratories, and sonographic characteristics are used to help stratify those nodules with an increased likelihood of malignancy, FNAB is currently the gold standard for tissue diagnosis. However, the rates of false-positive and false-negative results of FNAB represent a challenge in the management of patients with thyroid nodules, depending on the population studied. This study aimed to establish a profile of the ultrasound-guided thyroid fine-needle aspiration biopsies performed in our Puerto Rican population, which profile could be extrapolated to larger studies to help determine our population-based prevalence. Our study results point toward the need for additional tools, such as molecular markers, to improve our diagnostic and therapeutic decisions.

Resumen

Objetivo: Se buscó establecer un perfil clínico de las biopsias por aspiración con aguja fina (AAF) de nódulos de tiroides realizadas en las clínicas de endocrinología del Hospital Universitario de Puerto Rico. Métodos: Se realizó un estudio retrospectivo en todas las biopsias por AAF realizadas del 1 de julio de 2011 al 31 de diciembre de 2013. Datos sobre la demografía, citologías, cirugías y resultados histopatológicos fueron recopilados de los expedientes médicos. La prueba de Chi cuadrado se utilizó para establecer asociación entre los predictores y resultados, mientras que la prueba de McNemar fue aplicada para comparar los resultados citológicos e histopatológicos. Resultados: Se incluyeron un total de 240 AAF en 192 pacientes, de estos un 91.2% eran mujeres. La distribución citológica fue: 181 (75.4%) Benignos; 39 (16.3%) No-Diagnósticos; 15 (6.3%) Indeterminados; y 5 (2.1%) Malignos. Aquellos pacientes con citologías malignas eran usualmente menores de 45 años de edad (p=0.01) y fumadores (p=0.02). Los resultados histopatológicos estaban disponibles para 38 nódulos; no se encontró diferencia significativa entre la citología y la histopatología final. La sensibilidad y especificidad para las AAF fueron 75% y 100%, respectivamente. En aquellos nódulos con una citología inicial indeterminada (47%), 71% tuvieron una histopatología final benigna. Conclusión: En nuestro estudio, la mayoría de las AAF tuvieron una citología inicial benigna. Hubo un alto grado de concordancia entre las citologías e histologías. En aquellos nódulos con una citología indeterminada, la mayoría tuvo un resultado final histopatológico benigno. Estos datos sugieren la necesidad de implementar otras modalidades, como marcadores moleculares, para mejorar nuestras estrategias diagnósticas y terapéuticas, de acuerdo a nuestra prevalencia de enfermedad de base poblacional.

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