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The Role of Ultrasound, Scintigraphy, and Cytology in Evaluating Thyroid Nodules

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Abstract

BACKGROUND: Thyroid function testing and imaging studies guide the initial management of thyroid nodules. Our study aims to assess the role of ultrasound (US) and scintigraphy in the management of thyroid nodules.

METHODS: We conducted a prospective case series study of 212 consecutive patients presented with thyroid nodules at the tertiary University Hospital of Tirana (“Mother Teresa”) for further evaluation between January 2018 and March 2018. All patients were examined with US and scintigraphy with ^{99m}Tc and underwent fine-needle aspiration cytology. Generalized linear model (ordinal logistic) was used to predict the dependent variable with “ordered” multiple categories and independent variables.

RESULTS: The majority of patients (85%) were females, and (15%) males, $p < 0.001$. The ordered log it for US finding’s presence of micro-calcifications, adenopathy, solid,or solid-cystic nodules, being in a higher category of 2014 Italian Reporting System for Thyroid Cytology (TIR) was 1.27, 4.56, 2.70, and 1.70 more than absence of micro calcifications, adenopathy and cystic nodules, respectively. Conversely, a one unit (year) increase in age would result in a 0.035 unit decrease in the ordered log-odds of being in a higher TIR category. For the scintigraphy findings, the ordered log it for isohypofunctional and hypofunctional nodules (vs. isofunctional), in a higher TIR category, was 1.70 and 2.10 higher, respectively.

CONCLUSIONS: In thyroid glandular nodules, only a small percentage are malignant, therefore examination with US, scintigraphy and fine-needle aspiration (FNA) are important to lower the number of patients undergoing surgery. Given the study’s results, scintigraphy has a significant value, but to diagnose malignant nodules US remained an initial and important diagnostic tool, which, when combined with fine-needle aspiration cytology, rounds out a clear diagnosis of thyroid nodules.

Introduction

Thyroid nodules are defined as discrete lesions within the thyroid gland, radiologically distinct from the surrounding thyroid parenchyma [1]. Nodules may be solitary, multiple, cystic, or solid. The risk of thyroid nodules is higher with increasing age, female gender, iron deficiency, and history of thyroid radiation [2]. Thyroid nodules are approximately 3–4 times more common in women than men and occur more often in individuals living in iodine-deficient geographic areas [3], [4]. Thyroid glandular nodules are found in 4–10% of the population, but only 5–15% of them are malignant [5], [6], [7]. Thyroid glandular nodules are evidenced in 30–50% of the patients through and around 50% using scintigraphy [8], [9]. Initial evaluation for patients with a thyroid nodule should include these key components: Clinical history, physical examination, measurement of thyroid stimulating hormone (TSH), and thyroid ultrasound (US) to characterize the nodule and indicated fine-needle aspiration cytology (FNAC). Thyroid scintigraphy is the only technique that permits evaluation of the functional characteristics of a nodule using (^{99m}Tc) [9], [10], [11]. A cold nodule (hypofunctional) has reduced tracer uptake, a warm nodule (isofunctional) has tracer uptake roughly equivalent to the non-nodular tissue, and a hot nodule (hyperfunctional) has increased tracer uptake. The role of scintigraphy is to detect hypoechoic nodules as the incidence of malignant pathology is more frequent in hypoechoic nodules (5–15%) [1], [12], [13]. US has been more effective tool in diagnosing thyroid nodules (solid, cystic or solid-cystic characteristics, contours, microcalcifications, vascularity, and the rhythm of the volume’s growth of nodules), giving this way valid characteristics on benign and malign nodules [10], [13]. FNAC is a diagnostic procedure often used as one of the initial screening tests in thyroid nodules. Many studies have shown that following the introduction of Fine Needle Aspiration (FNA), the number of thyroid surgical procedures has decreased [14].

Methods

This was a prospective case series study. We observed a total of 212 consecutive patients presented at the University Hospital Center: “Mother Teresa”, Tirane, Albania during January 2018–March 2018. They were all examined with US and scintigraphy with of ^{99m}Tc and underwent ultrasound guided FNA cytology.

Procedure

Thyroid scintigraphy was done after injecting 80 MBq of ^{99m}Tc pertechnetate. The images were taken after 20 min of anterior positioning. The US was done with linear probe of 7–9 MHz, with the patients laying with head in extension. FNA was conducted under US guidance with a needle 23–25G, using a sterilized syringe of 10 or 20 ml. The aspiration was done with a sequential move of the syringe in the anteroposterior direction. The aspirated material was fixed in laboratory glass slides and was then taken immediately to the pathologist for further cytological evaluation. Efforts were made to prevent antiaggregant and anticoagulant effects before the procedure to increase the success rates of the procedure.

Data analysis

The corresponding frequencies and percentages were calculated to describe the category variables. The one sample proportional test was used to determine if the population proportion of one level in a binary variable equals a specific claimed value (50%). Generalized linear model (GLM) (ordinal logistic) was used to predict the dependent variable with “ordered” multiple categories and independent variables. Predictive variables used for this model were (age, gender, nodes size and structure, accompanying conditions, post thyroidectomy status, nodes numbers, calcification, lymphnodes, adenopathy’s presence, and echogenicity of nodes). This model was selected because the assumption of the ordinal logistic regression that the relationship between each pair of outcome groups should be the same was violated. Multivariable-adjusted estimates (beta coefficients), 95% CIs and p-values were calculated. $p \leq 0.05$ was considered statistically significant. Statistical analysis was conducted using Statistical Package for the Social Sciences, statistical software, version 21.0.

Ethical considerations

All the participants gave their oral consent for the anonymous use of their data for research purposes.

Results

All 212 patients included in our study underwent scintigraphic, US, and FNA evaluation for assessment of their thyroid nodules. The majority of patients (85%) were female, and (15%) men, $p < 0.001$. Most patients did not have other accompanying conditions (67%), while (33%) had accompanying pathologies [Table 1].

The majority of nodules were solid nodules (80%), with the rest being solid-cystic (16%), and cystic (4%). The thyroid scan results showed, most of the examined nodules were hypoechoic nodules (cold), followed by isoechoic and less isohyperechoic nodules [Table 1].

The results of GLM (ordinal logistic) are given in Table 3. The thyroid cytology (TIR) system of reporting TIR (The 2014 Italian Reporting System for TIR) was used for reporting FNAC specimens of the thyroid. The parameter used to determine the satisfactoriness of the specimens was the presence of at least six clusters of thyroidal follicular cells, with each cluster including at least 10 follicular cells with good preservation. There was a higher frequency of TIR 2 and TIR 3 results, with less cases diagnosed as TIR 4 and TIR 5. A small number of them were classified as unsatisfactory or TIR 1. The ordered logit for US

Table 1: Baseline characteristics

Baseline characteristics	n (%)*	p-value
Age		
<50 years	93 (43.9)	
>50 years	119 (56.1)	0.086
Gender		
Males	32 (15.1)	<0.001
Females	180 (84.9)	
Accompanying conditions		
Present	70 (33.0)	N/A†
Non-present	142 (67.0)	
Post thyroidectomy		
Yes	7 (3.3)	N/A
No	205 (96.7)	
Cytology (reexamination)		
Yes	4 (1.9)	N/A
No	208 (98.1)	

*Absolute numbers and their respective percentages. †Non applied.

Table 2: Characteristics of nodules

Characteristics of nodules	N (%)*
No. of nodules	
1	144 (67.9)
2	43 (20.3)
3	12 (5.7)
>3	13 (6.1)
Nodule size	
1.0–1.9 cm	4 (1.9)
2.0–2.9 cm	14 (6.6)
3.0–3.9 cm	21 (9.9)
>4.0 cm	173 (81.6)
Echogenicity	
Hyperechogenicity	15 (7.1)
Hypoechogenicity	47 (22.2)
Isoechogenicity	69 (32.5)
Iso hyperechogenicity	16 (7.5)
Iso hypoechogenicity	65 (30.7)
Structure	
Solid	170 (80.2)
Cystic	9 (4.2)
Solid cystic	33 (15.6)
Microcalcifications	
Yes	94 (44.3)
No	118 (55.7)
Lymph nodes	
Yes	103 (48.6)
No	109 (51.4)

Table 3: Results from generalized linear model (ordinal logistic), with the dependent variable (TIR categories)

Parameters of items	Independent variables	Estimate	Std. Error	Wald	df	Sig.	95% Confidence interval	
							Lower bound	Upper bound
Threshold	TIR = 1	−0.269	1.183	0.052	1	0.820	−2.588	2.049
	TIR = 2	2.802	1.204	5.421	1	0.020*	0.443	5.161
	TIR = 3	5.253	1.242	17.893	1	0.000*	2.819	7.687
	TIR = 4	7.476	1.320	32.080	1	0.000*	4.889	10.064
Location	Age	−0.035	0.013	6.660	1	0.010*	−0.061	−0.008
	Nodus size	0.017	0.014	1.470	1	0.225	−0.010	0.044
	Female	0.017	0.403	0.002	1	0.967	−0.774	0.807
	Male	0^a	.	.	0	.	.	.
	Accompanying conditions - Yes	−0.038	0.386	0.010	1	0.921	−0.795	0.719
	Accompanying conditions - No	0^a	.	.	0	.	.	0
	Posthyroid-ectomy - Yes	−0.692	0.850	0.664	1	0.415	−2.357	0.973
	Post thyroidectomy - No	0^a	.	.	0	.	.	0
	Nodus number>3	1.191	0.613	3.777	1	0.052	−0.010	2.392
	Nodus number = 3	−0.317	0.621	0.260	1	0.610	−1.534	0.900
	Nodus number = 2	0.047	0.357	0.017	1	0.896	−0.652	0.746
	Nodus number = 1	0^a	.	.	0	.	.	0
	Microcalcifications - Yes	1.266	0.327	14.952	1	0.000*	0.624	1.907
	Microcalcifications - No	0^a	.	.	0	0	0	0
	Lymph nodes - Yes	0.142	0.310	0.210	1	0.647	−0.465	0.749
	Lymph nodes - No	0^a	.	.	0	.	.	0
	Adenopathy - Yes	4.557	1.284	12.601	1	0.000*	2.041	7.073
	Adenopathy - No	0^a	.	.	0	.	.	0
	Solid	2.697	0.790	11.649	1	0.001*	1.148	4.246
	Solid cystic	1.696	0.808	4.410	1	0.036*	0.113	3.280
	Cystic	0^a	.	.	0	.	.	0
	Iso hyperechoic	0.655	0.550	1.418	1	0.234	−0.423	1.732
	Iso hypoechoic	−0.629	0.362	3.028	1	0.082	−1.338	0.080
	hyperechoic	−0.699	0.629	1.235	1	0.266	−1.933	0.534
	hypoechoic	−0.266	0.432	0.379	1	0.538	−1.113	0.581
	Isoechoic	0^a	.	.	0	.	.	0
	Isohyperfunctional	−0.468	0.641	0.534	1	0.465	−1.723	0.787
	Isohypofunctional	1.700	0.448	14.392	1	0.000*	0.822	2.579
	hyperfunctional	0.982	0.836	1.379	1	0.240	−0.657	2.621
	hypofunctional	2.100	0.440	22.742	1	0.000*	1.237	2.963
	Isofunctional	0^a	.	.	0	.	.	0

*Significance at p ≤ 0.05.

finding's presence of microcalcifications, adenopathy, solid, and solid cystic nodules, being in a higher TIR category was 1.27, 4.56, 2.70, and 1.70 more than absence of micro-calcifications, adenopathy, and cystic nodules, respectively. Conversely, a one unit (year) increase in age would result in a 0.035 unit decrease in the ordered log-odds of being in a higher TIR category. For the scintigraphy findings, the ordered logit for isohypofunctional and hypofunctional nodules (vs. isofunctional), in a higher TIR category, was 1.70 and 2.10 higher, respectively. Meanwhile, the results for the presence of more than 3 nodules (vs. 1 nodule) were almost significant, with the increase of the estimate by approximately 1.20 (p =0.052).

Discussion

Most thyroid nodules are benign, usually as a part of multinodular changes. The primary goal in the management of a thyroid nodule is to identify the small group of patients in whom the nodule is malignant and would benefit from early aggressive treatment while avoiding unnecessary investigation and surgery in the majority of patients who have a benign nodule. Consequently, the purpose of this study was to estimate and define the role of US and scintigraphy in the process of patient selection for US guided FNA. Our study showed that there is a statistically significant difference in representation of nodular changes with different genders (85% women and 15% men, p < 0.001). This is also reinforced with literature findings, which acknowledge frequency of thyroid nodule occurrence to be about 3 times higher in women than in men [15]. It is known from the literature that thyroid cancer can occur at any age, but approximately two-thirds of all cases are found in people in between 20 and 50 [16]. This can be one of the reasons why, after applying the GLM (ordinal logistic) model in our study, the increase in age was accompanied by a decrease in the likelihood of a higher TIR classification. According to our study, there is no significant difference between numbers of patients with nodules <50 years of age and those above 50 years of age. Our study did not show significant differences, with respect to the increase in TIR, in terms of nodules size, concomitant diseases, post-thyroidectomy condition and the presence of non-pathological lymph nodules. In fact, another study showed that the highest risk of malignancy was observed in nodules <2 cm and no increase in the risk of malignancy in nodules >2 cm [17]. Based on the literature results, micro-calcifications on US can be a potential predictor of thyroid nodule malignancy [18]. Our study showed that the presence of microcalcifications provides 1.21 times greater likelihood for higher TIR categories. Findings from another study showed that the risk of nodular malignancy with minimal cystic changes was significantly lower than that of purely solid nodules (p = 0.013) [19]. Our study also showed that the solid or solid cystic structure of the nodule was more likely to increase the TIR categories than its cystic structure.

Sonographically detected nodules were subsequently also classified by their

99mTc-pertechnetate uptake in the thyroid scintigraphy as either hypofunctional (below the level of the surrounding thyroid tissue), or hyperfunctional (above the level of the surrounding thyroid tissue). Nodules qualified as "hot" in 99mTc-pertechnetate scintigraphy showed an increased uptake of the radioisotope and were qualified as benign. Thus in a retrospective evaluation, approximately 90% of the benign nodules (FNAC results) in our study were hyperfunctional (hot) according to scintigraphy results. Given the low malignancy risk of hyperfunctional nodules, thyroid scintigraphy therefore provides complementary diagnostic information to sonography. Consequently, scintigraphy proven warm nodules do not require cytological puncture. In our study, the majority of patients with FNAC reports of TIR 4 and TIR 5 according to TIR system had hypoechoic nodules (cold nodules).

The results in our study were close to those reported by similar studies in the literature. There was no significant association found in the US description of nodules (isoechoic, hypoechoic, hyperechoic, hypoisoechoic, and hyperisoechoic) with TIR categories, necessitating the standardization of the terminology used by radiologists when reporting thyroid gland nodules. This study is important because it compares the three diagnostic tools for thyroid nodules, in the context of the most accurate differential diagnosis. It is evident that we are in the era of diagnosis with FNA cytology, again emphasizing the rare use of scintigraphy in the work-up of a nodule, even due to radiation and extra costs [20]. However, in the multivariate analysis of this study, when the US characteristics were adjusted with the scintigraphic characteristics, the results of the scintigraphy were significantly predictive. It is important to mention that these significant predictive values of scintigraphy are valid for the transition to the ordinal categories of TIR and not for a dichotomized outcome variable (benign vs. malignant). Other studies may be valuable in that the presence or absence of a low TSH value will be studied concurrently in the study population.

Conclusions

In thyroid gland nodules, only small percentage is malignant. Therefore, US examination, scintigraphy, and FNAC are important diagnostic steps that facilitate a personalized risk-based protocol that promotes high-quality care and avoidance of unnecessary surgery. Given the study's results, scintigraphy has a significant value, but to diagnose malignant nodules US remained an initial and important diagnostic tool, which, when combined with FNA, rounds out a clear diagnosis of thyroid nodules.

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