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HISTOPATHOLOGICAL STUDY OF SOLITARY THYROID NODULES IN A SAMPLE OF IRAQI PATIENT

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Summary

Objectives: To examine solitary thyroid nodules and their behavior, clinicopathological characteristics, age, sex, ultrasonography, Thyroid Imaging Reporting & Data System results (TIRADS), and cytological groupings (Bethesda).

Methods: A retrospective study includes 100 solitary thyroid nodules from archives of Medical city labs between 2021 and 2023. TIRADS and Bethesda categories were recorded when accessible. Radiology records were provided for 98 patients and cytology for 21.

Results: The average age of patients was 37.5±11.8 years, with a male-to-female ratio of 1:4.7. The nodules were 67% benign, 22% malignant, and 11% low-risk. The most prevalent pathological diagnosis of single nodules was colloid nodules (45%) followed by papillary carcinoma (16%). Twenty-two present of single thyroid nodules were malignant, all were well-differentiated. In ultrasonography, TIRADS classifications 3-5, malignancy risk was 4.7%, 30.8%, and 53.3%. The risk of malignancy for Bethesda 2-5 was 0, 14.3%, 25%, and 100%. All malignancies were in adults with 1:4.5 female predilection. No significant association was seen in patient's age, sex, or nodule side. Ultrasound had greater sensitivity (90.9% vs 85.7%), while cytology was more specific (76.9% vs 64.6%) and had a larger positive predictive value (66.7% vs 46.5%). Cytology was more accurate than ultrasonography (80% vs 71.3%).

Conclusion: There was a 22% risk of cancer in solitary thyroid nodules, all were well-differentiated. Bethesda was more precise, while ultrasound was more sensitive.

KEYWORDS: *thyroid, solitary nodule, risk of malignancy, Bethesda, TIRADS*

INTRODUCTION

Solitary thyroid nodules are common. Asymptomatic nodules of 1 cm or more are reported in 50% of autopsies(1). Being an extremely frequent finding in the general population, thyroid nodules enter the spectrum of the most common diagnostic dilemmas in endocrine surgery, cytology, and surgical pathology. By palpation, such nodules can be found in 3.7–7% of the general population, more frequently in females: 6.4% contrasting with 1.5% in males. Three-quarters of palpable nodules are solitary, raising increased suspicion of neoplasm(2).

Recent data suggest that the incidence of thyroid malignancy has increased over the years. In Iraq, thyroid cancer incidence grew from 1.22 to 2.96 per 100,000 during the period between 2000–2016, with a sharp spike in 2007(3). This is consistent with the global trend of low– and middle-income nations and regional countries such as Iran (2.2/100 000)(4) and Jordan (2.6/100 000)(5). Although the precise reasons for the increase are not fully known, it is possible that they are related, at least in part, to the advent of new diagnostic methods (e.g., ultrasonography, thyroid scans, and fine-needle aspiration biopsy) and improvements

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in cancer registration practices(6), however, a true increase in the incidence of papillary thyroid carcinoma (PTC) has also been suggested.

Both solitary and multinodular goiters are associated with malignancy. Some studies linked solitary nodules to a greater malignancy risk than multinodular goiters, yet this is an area of dispute(7). The characteristics of solitary thyroid nodules in the Iraqi population have been described previously in the late sixties and seventies from a management point of view(8,9). A more recent study reported 7.4% cancer risk in solitary thyroid nodul (10), however, none looked into the histological subtypes and cancer risk in each cytological and radiological standardized reporting category.

Management of solitary thyroid nodule is multidisciplinary. The American Thyroid Association recommendation and the American College of Radiology Thyroid Imaging Reporting and Data System (TIRADS) are the most extensively used risk categorization methods for thyroid nodules. Fine needle aspiration biopsy (FNA) is the gold standard for nodule assessment. The Bethesda System for Reporting Thyroid Cytopathology is the most used cytological categorization for FNAB. TBSRTC, modified in 2023, simplifies 6-category reporting (11,12). Surgery may be employed in the subsequent circumstances: Nodular symptomatic thyroid disease, Nodules that were initially deemed benign by cytology and/or ultrasound but subsequently manifest symptoms, Nodules exhibiting indeterminate cytology (classes III and IV Bethesda) render active surveillance impracticable. Cytology-determined nodules of Bethesda classes V and VI(13).

The study aims to evaluate benign and malignant solitary thyroid nodules through clinicopathological parameters, age, sex, ultrasound findings (TIRADS), and cytological groups (Bethesda).

METHODS

This retrospective observational study was conducted at Baghdad Medical Teaching Hospital and Teaching Laboratories between Jan 2023 and Dec 2023. The archive of histopathology department was searched for thyroidectomies and lobectomies with solitary thyroid nodule. A total of 100 successive cases were collected with complete histopathology reports and slides. The exclusion criteria included incomplete pathology reports or unavailability of histopathology slides. Radiological reports were available for 98 cases, while only 21 cases had cytology reports. When available, TIRADS and Bethesda categories were recorded. All slides were evaluated by a Board certified pathologist, who affirmed the final diagnosis. The demographic information, size, and location of the nodule were extracted from the patients' medical records.

Procedures were in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki Declaration of 1975, (as revised in 2000). It has been registered with the identification number (EAC: 2541)

Statistical analyses were performed using IBM SPSS software version 25, with Chi-square tests or Fisher's exact tests used to assess proportions of nominal/ ordinal variables.

Risk of malignancy (ROM) was calculated by dividing the malignant cases in each category by the total number of cases in the same category. The denominator was restricted to the malignant cases, ie low-risk tumors were not considered as malignant.

To assess the validity of ultrasound and cytology, TIRADS II and III in the US and Bethesda II and III by cytology were grouped as benign while TIRADS IV and V and Bethesda IV and V were grouped as malignant. Histopathology was considered the gold standard; however, low-risk neoplasm cases were excluded.

RESULTS

Patients and solitary nodule characteristics

A total of 100 cases were retrospectively collected, 83% were female, 1:4.7 male-to-female ratio. The patients' average age was 37.5 (±11.8) years, ranging from 14 to 73 years, with only 4% under 20 years old. Imaging and cytology reports were accessible for 98% and 21% of patients in the pathology archive. Right-lobe single nodules were 56% and isthmus nodules were 3%. The ultrasound mean nodule size was 25.94 mm, similar to the grossing mean. Details are shown in Table 1.

Classification of the solitary nodules

As Figure 1 shows, (67%) of the nodules were benign, (22%) were malignant and (11%) were

Table 1.

Demographics and characteristics of the study group.

Variable		Frequency	Percent (%)
Age	<20	4	4
	20-54	88	88
	>=55	8	8
Sex	F	83	83
	M	17	17
Site	Left	41	41
	Right	56	56
	Isthmus	3	3
size (mm) mean (± SD)	US	25.94	(18.13)
	Gross	25.94	(19.54)
US data availability	No	2	2
	Yes	98	98
Cyto data availability	No	79	79
	Yes	21	21

low-risk neoplasm. The most common pathological diagnosis of the solitary nodules was colloid nodules (45%) followed by PTC.

Follicular nodular disease represented more than half of the collected cases distributed as 1% cyst, 45% colloid, and 5% thyroiditis. Follicular adenomas were more frequent than follicular carcinomas (14% vs 3%) while oncocytic carcinomas were more frequent than oncocytic adenomas (3% vs 2%).

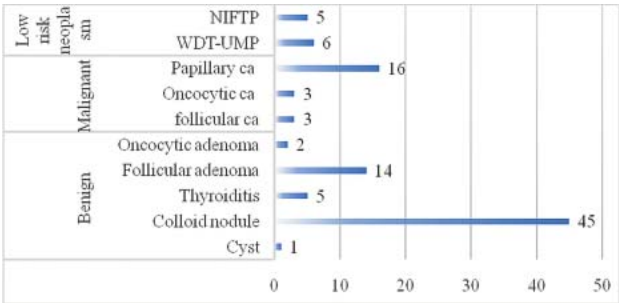

Figure 1: Histopathology type of solitary thyroid nodules.

Risk of malignancy (ROM) in ultrasound and cytology categories for solitary thyroid nodules

The total risk of malignancy in solitary thyroid nodules was (22%). For ultrasound TIRADS categories, ROM for TIRADS 3-5 were (4.7%, 30.8%, and 53.3%) respectively, and no malignancy was reported in TIRADS 2 nodules. More than half (54.5%) of malignant tumors and the majority (81.8%) of low-risk tumors were reported as TIRADS 4 nodules pre-operatively, Table 2. Five out of 15 (33.3%) of the nodules in TIRADS 5 turned out to be benign after excision, however, 3 of them were adenomas as further detailed in Table 3.

Preoperative cytology reports could be collected for less than a quarter of the cases. The ROM for Bethesda 2-5 was 0, 14.3%, 25%, and 100% respectively, Table 2.

Table 2.

Association of pre-surgical US and cytology classifications and nodule behavior according to final histopathology diagnosis.

			Tumor behavior							
Classification	**Total No.**	**%**	**Benign No.**	**%**	**Malignant No.**	**%**	**Low-risk neoplasm No.**	**%**	**P value**	**ROM* (%)**
Ultrasound										
TIRADS 2	2	2.0%	2	3.1%	0	0.0%	0	0.0%	<0.001	0%
TIRADS 3	42	42.9%	40	61.5%	2	9.1%	0	0.0%		4.7%
TIRADS 4	39	39.8%	18	27.7%	12	54.5%	9	81.8%		30.8%
TIRADS 5	15	15.3%	5	7.7%	8	36.4%	2	18.2%		53.3%
Total	98	100%	65	100%	22	100%	11	100%		21.4%
Cytology										
Bethesda 2	5	23.8%	4	30.8%	0	0%	1	100%	0.003	0
Bethesda 3	7	33.3%	6	46.2%	1	14.30%	0	0.%		14.3%
Bethesda 4	4	19%	3	23.1%	1	14.30%	0	0.%		25%
Bethesda 5	5	23.8%	0	0.%	5	71.40%	0	0%		100%
Total	21	100%	13	100%	7	100%	1	100%		33.3%

Low-risk neoplasms were not considered malignant.

Table 3.

Association of pre-surgical US and cytology classifications and final histopathology type.

Tumor type																				
Classification	**Total**	**%**	**Colloid nodule**	**%**	**Thyroiditis**	**%**	**Follicular adenoma**	**%**	**Oncocytic adenoma**	**%**	**follicular carcinoma**	**%**	**Oncocytic carcinoma**	**%**	**Papillary carcinoma**	**%**	**WDT-UMP**	**%**	**NFTP**	**%**	**P value**
Ultrasound -TIRADS																				
TR 2	2	2	2	4.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
TR 3	42	42.9	30	66.7	4	80	5	38.5	1	50	0	0	0	0	2	12.5	0	0	0	0	<0.001
TR 4	39	39.8	12	26.7	0	0	6	46.2	0	0	2	66.7	1	33.3	9	56.3	5	83.3	4	80	
TR 5	15	15.3	1	2.2	1	20	2	15.4	1	50	1	33.3	2	66.7	5	31.3	1	16.7	1	20	
Total	98	100	45	100	5	100	13	100	2	100	3	100	3	100	16	100	6	100	5	100	
Cytology – Bethesda																					
B 2	5	23	3	42.9	0	0	1	25	0	0	0	0	0	0	0	0	-		1	100	
B 3	7	33.3	3	42.9	1	100	2	50	0	0	0	0	0	0	1	25	-		0	0	0.133
B 4	4	19	1	14.3	0	0	1	25	1	100	0	0	1	50	0	0	-		0	0	
B 5	5	23	0	0	0	0	0	0	0	0	1	100	1	50	3	75	-		0	0.0	
Total	21	100	7	100	1	100	4	100	1	100	1	100	2	100	4	100	-		1	100	

Table 4.

Association of different variables and nodule behavior.

Tumor behavior										
Variable		**Total No.**	**%**	**Benign No.**	**%**	**Malignant No.**	**%**	**UMP No.**	**%**	**P value**
Age groups	<20	4	4.0%	4	6.0%	0	0.0%	0	0.%	0.588
	20-54	88	88.0%	58	86.6%	19	86.4%	11	100.%	
	>=55	8	8.0%	5	7.4%	3	13.6%	0	0%	
Sex	F	83	83.0%	54	80.6%	18	81.8%	11	100%	0.294
	M	17	17.0%	13	19.4%	4	18.2%	0	0%	
Side	Left	41	41.0%	22	32.8%	14	63.6%	5	45.5%	0.209
	Right	56	56.0%	42	62.7%	8	36.4%	6	54.5%	
	isthmus	3	3.0%	3	4.5%	0	0.0%	0	0%	
Type of operation	Lobectomy	34	34.3%	27	40.3%	5	22.7%	2	18.2%	0.375
	Total thyroidectomy	63	62.6%	37	55.2%	17	77.3%	9	81.8%	
	subtotal thyroidectomy	3	3.0%	3	4.5%	0	0.0%	0	0%	

Abbreviations: UMP: uncertain malignant potential

Table 5.
Validity of cytology and ultrasound tests in evaluating solitary thyroid nodule relative to surgical pathology as the gold standard.

Surgical pathology				
Test		Malignant	Benign	Total
Cytology	Bethesda IV&V	6 (85.7%)	3 (23.1%)	9 (45%)
	Bethesda II&III	1 (14.3%)	10 (76.9%)	11 (55%)
	Total	7 (100%)	13 (100%)	20 (100%)
Sensitivity		85.70%		
Specificity		76.90%		
PPV		66.70%		
NPP		90.90%		
Accuracy		80%		
Ultrasound	TIRADS IV&V	20 (90.9%)	23 (35.4%)	43 (49.4%)
	TIRADS II&III	2 (9.1%)	42 (64.6%)	44 (50.6%)
	Total	22 (100%)	65 (100%)	87 (100%)
Sensitivity		90.90%		
Specificity		64.60%		
PPV		46.50%		
NPP		95.50%		
Accuracy		71.30%		

* Cases of Uncertain malignant potential were excluded. Abbreviation: PPV, positive predictive value; NPP, negative predictive value

One case out of five evaluated as Bethesda 2 preoperatively turned out to be NIFTP while two out of the three benign cases reported as Bethesda 4 were diagnosed with adenoma after excision as shown in Table 3.

Demographic and clinical correlation with solitary nodule behavior

When the nodules are classified according to their behavior, all malignant tumors were in adult patients with female predilection 1:4.5. No significant correlation was seen in patient age (P= 0.588), sex (P=0.294), nodule side (P=0.209), or surgical procedure (P=0.375); as shown in Table 4.

Validity of ultrasound and cytology tests in evaluating solitary thyroid tumors pre-operatively

The sensitivity of ultrasound was higher than cytology (90.9% vs 85.7%) whereas cytology was more specific (76.9% vs 64.6%) with higher PPV (66.7% vs 46.5%). The overall accuracy of the cytology test was higher than US (80% vs 71.3%) (Table 5)

DISCUSSION

The characteristics of solitary thyroid nodules in the Iraqi population have been described previously in the late sixties and seventies from a management point of view (8, 9). An Iraqi review of 489 thyroidectomies reported(12.9%) solitary nodules between 2015 and 2016(14). A more recent study reported 7.4% cancer risk in solitary thyroid nodules(10), however, none looked into the histological subtypes and cancer risk in each cytological and radiological standardized reporting category.

Females predominated in the current study with a male-to-female ratio of 1:4.7. Euthyroid nodular goiter is generally more prevalent in women(15); similar prevalence was reported by several other local studies from northern and middle parts of Iraq ranging between (81-86.5%)(10,13-15).

The mean age of the patients in the current study was 37.5 (±11) with (4%) of the patients younger than 20 years. In agreement with that many studies reported that solitary nodules are common in adults. Research conducted on 78 patients with thyroid nodules in Babylon revealed

that the highest occurrence was seen during the third decade(16). A study prospectively investigated solitary nodules in Basrah reported a mean age of 44.3±4 years(17). By contrast, in a recent study conducted in Al Yarmouk Teaching Hospital, there was a significant number of young patients between the ages of 15 and 29 had a solitary thyroid nodule, accounting for (51.9%) of all patients(10).

In the current study, the rate of malignancy in solitary thyroid nodules was (22%), all were well-differentiated carcinoma (16% PTC, 3% oncocytic carcinoma, and 3% follicular carcinoma). In comprehensive research done by **Al-Hakami et al** (2020), it was shown that out of 987 individuals, the incidence of malignancy was notably greater in solitary nodules(18). A lower malignancy rate, however, was reported by **Noori et al**. (2017) who found that the malignancy rate in solitary thyroid nodules did not exceed 13.2%(17). The variable rate of malignancy reported in different studies is justified by the different inclusion criteria and study design, As an illustration, **Noori et al.** (2017) (17) conducted a study to collect clinically diagnosed solitary nodules. 13 out of 146 collected cases turned to be malignant with a malignancy rate of 8.9%. However, upon surgical pathology examination, 68 out of 146 (46.6%) of these nodules were confirmed to be true solitary; nine nodules of these (13.2%) were malignant.

The study found a low-risk neoplasm rate of 11%, with 5 NIFTP and 6 WDT-UMP cases. The litigation climate has led to overdiagnosis of WDT-UMP or EFV-PTC, as pathologists use flexible diagnostic criteria to avoid legal action. However, this method can result in overtreatment and patient psychological distress(19). A study conducted in Japan reviewed surgical pathology files of 2648 cases with thyroid lesions over a period of 10 years. The author concluded that the incidence of WDT-UMP in the thyroid specimens was (1.1%). In the same period, 501 cases (18.9%) of conventional PTC were diagnosed(19).

The development of advanced investigation and the growing use of ultrasonography have improved the diagnosis of thyroid nodules(20). The diagnostic performance of ACR-TIRADS of solitary thyroid nodules relative to final surgical in the current study revealed (90.9%) sensitivity and (64.6%) specificity. According to the literature, the sensitivity of ACR-TIRADS ranged between (76.1%-100%)(21-27) and specificity did not exceed (75.2%)(22). In a recent meta-analysis, Joo et al. (2023) examined 11 studies that evaluated the effectiveness of biopsy criteria in ultrasound scoring systems for risk stratification. The studies included a total of 27,250 nodules. The researchers concluded that the pooled sensitivity and specificity for ACR-TIRADS were (82% and 60%), respectively(28). This emphasizes the practical implication of ACR-TIRADS which is to identify nodules that require cytological evaluation rather than surgical excision. In the current study only two (4.7%) out of 42 TIRADS 3 cases were malignant on surgical pathology with a risk of malignancy of (4.7%) while 5 (33.3%) out of 15 TIRADS 5 were benign with a risk of malignancy of 53.3%. Hence surgical decisions based on TIRADS categories without cytological evaluation can increase the rate of unnecessary surgeries.

Fine needle aspiration cytology is a minimally invasive procedure that efficiently distinguishes malignant from benign thyroid nodules, hence avoiding needless surgery(29). The Bethesda system for FNA reporting is a good method for classifying thyroid nodules with high malignancy risk(30). According to the findings of a meta-analysis that was carried out by Bongiovanni et al. (2012), the distribution of patients who had undergone surgery according to the various Bethesda categories was as follows: (8.3%, 24.6%, 15%, 28.2%, 7.9%, and 16%), respectively, and the total rate of cancer was 33.8%(31). This was quite close to the overall risk of malignancy in the cytology groups (33.3%) of the current study, however, cytology reports were limited to less than a quarter of our sample.

The sensitivity and specificity of the Bethesda system in our series of solitary thyroid nodules were (85.7% and 76.9%) respectively and an overall accuracy of (80%). A meta-analysis of eight relevant studies with a 25,445 pooled number of patients calculated the sensitivity of Beth IV, V, and VI to be (97.0%) and the specificity to be (50.7%), while overall accuracy was (68.8%)(31). The major contributor to the low specificity of the Bethesda reporting system is the Bethesda IV category. We had three false positive cases all were Bethesda IV which by definition cannot differentiate between follicular carcinoma and benign follicular adenoma(32). A Colombian study observed substantial variance in the malignancy risk of category IV, with oncology centers reporting a value of (56.3%) and

nononcologic centers reporting (23.5%). This variation was ascribed to the selection bias that favored patients requiring surgery(33). The present research found that the ROM in cases classified as Bethesda 5 was (100%), while it was (25%) for Bethesda 4 and (14.3%) for Bethesda 3. In comparison to the literature, we had lower ROM in Bethesda 3 but higher in Bethesda 5. This may be attributed, at least in part, to the solitary character of the nodules gathered in the present investigation. The meta-analysis conducted by Bongiovanni et al. (2012) revealed the rate of malignancy according to the different Bethesda categories as follows: 16.8% (Beth I), 3.7% (Beth II), 15.9% (Beth III), 26.1% (Beth IV), 75.2% (Beth V) and 98.6% (Beth VI)(31).

As the study was designed to retrospectively collect the cases, the incomplete cytological and radiological report was the main limitation.

CONCLUSION

The majority of solitary thyroid nodules were found in female patients, with over one-fifth of resected nodules being malignant. The majority are well-differentiated tumors, with papillary carcinoma being the most common. Ultrasound is more sensitive, while FNAC cytology is more specific.

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Sažetak

HISTOPATOLOŠKA STUDIJA SOLITARNIH ČVOROVA ŠTITNJAČE NA UZORKU PACIJENTA IZ IRAKA

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Ciljevi: ispitati solitarne čvorove štitnjače i njihovo ponašanje, kliničko-patološke karakteristike, dob, spol, ultrazvuk, rezultate Tiroid Imaging Reporting & Data System (TIRADS) i citološke skupine (Bethesda).

Metode: Retrospektivna studija uključuje 100 pojedinačnih čvorova štitnjače iz arhiva Medical city labsa između 2021. i 2023. godine.

Rezultati: Prosječna dob bolesnika bila je 37,5 ±11,8 godina, s omjerom muškaraca i žena 1:4,7. Čvorovi su bili 67% benigni, 22% maligni i 11% niskorizični. Najčešće patološke dijagnoze pojedinačnih čvorova bile su koloidni noduli (45%) ipapilarni karcinom (16%). Dvadeset i dva čvora štitnjače bila su zloćudna, a svi su bili dobro diferencirani. Kod ultrazvučnih nalaza TIRADS klasifikacije 3-5, rizik malignosti bio je 4,7%, 30,8% i 53,3%. Rizik zloćudnosti za citološku Bethesda klasifikaciju 2-5 bio je 0, 14,3%, 25% i 100%. Sve zloćudne bolesti bile su u odraslih s predilekcijom žena 1:4,5. Nije uočena značajna povezanost u dobi, spolu ili strani čvora. Ultrazvučni nalaz imao je veću osjetljivost (90,9% prema 85,7%), dok je citološki nalaz pokazao veću specifičnost (76,9% prema 64,6%) i pozitivnu prediktivnu vrijednost (66,7% prema 46,5%). Citološki nalaz bio je precizniji od ultrazvučnog (80% prema 71,3%).

Zaključak: postojao je 22% rizik od raka kod solitarnih čvorova štitnjače, svi su bili dobro diferencirani. Citološki nalaz po Bethesda klasifikaciji bio je precizniji, dok je ultrazvučni nalaz uz korištenje TIRADS klasifikacije bio osjetljiviji.

KLJUČNE RIJEČI: *štitnjača, solitarni nodus, rizik od maligniteta, Bethesda, TIRADS*