Prospective study evaluating malignancy in solitary thyroid nodule

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Objective
The aim of this study was the preoperative evaluation of patients with solitary thyroid nodules (STNs) for the presence of malignancy to avoid unnecessary total thyroidectomy.
Patients and methods
A total of 83 patients with STNs who underwent hemithyroidectomy, total thyroidectomy, and total thyroidectomy with modified neck dissection in Ain Shams University Hospitals and Helwan University Hospital between September 2016 and December 2017 were evaluated. Parameters including demographics, ultrasonographic, and pathological data were analyzed.
Results
After evaluation of the final pathology, results showed that malignancy was found in 33/83 (39.8%) patients. A total of 24 (72.7%) of these lesions were papillary carcinoma. Multinodular goiter accounted for 90% of all benign cases. Of 19 malignant cases, 14 (73.7%) were males, whereas of 64 benign cases, 45 (70.3%) were female patients. Nodule echogenicity, nodule calcification, nodule vascularity, nodule shape, and nodule margins were found to have significant prediction for malignancy. Among these factors, increased vascularity and irregular nodule margins were the most important factors. Nodule size did not affect the risk of malignancy. Moreover, lymph node characteristics were found to have significant prediction for malignancy. The FNA results of BII-V reports showed that 17.2% of patients with STN nodule had false negative results.
Conclusion
Multivariate analysis revealed that in STN, the highest malignancy predictor was the 'No halo and irregular Margin' in ultrasound, and that microcalcifications, hypoechoic, and taller nodules were highly suspicious factors for malignancy.

Keywords:
hemithyroidectomy, solitary thyroid nodule, total thyroidectomy

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Introduction

Solitary thyroid nodule (STN) is one of the common thyroid presentation, and approximately 8% of the adult population presents with clinically palpable thyroid nodules [1]. Use of imaging techniques, particularly ultrasound, has increased the chance of detection of the thyroid nodules greatly [2]. Patients with STN must be further evaluated for other nodules [3]

The reported incidence of thyroid cancer in general population is low, being approximately 1%. Thyroid cancers occur in ~5% of all thyroid nodules independent of their size [4]. The occurrence of malignancy is more in STNs compared with multinodular goiter [5].

The preoperative evaluation of thyroid nodules to distinguish between benign and malignant nodules is very important. It helps to avoid unnecessary extensive surgery and potential surgery-related adverse effects, such as hypothyroidism, hypocalcemia, and recurrent laryngeal nerve injury [6].

Hypothesis

The aim of this study was to evaluate patients with STN for the presence of malignancy, in relation to various factors like age, sex, and ultrasonography findings like size of the nodule, echogenicity, microcalcification, and presence of lymphadenopathy to detect various malignancy predictors to avoid unnecessary extensive surgery and its complications.

Patients and methods

Patients

This study was conducted in Endocrine-Surgery Unit of Ain-Shams University Hospital and Helwan University Hospital on 83 patients who underwent surgery for STN between September 2016 and December 2017.

The study group consisted of 83 patients who presented with clinically palpable STN and confirmed radiologically by ultrasound.

Written informed consent was obtained from all patients before being assigned to surgery.

Preoperative

The surgical details and complications of different procedures including hemithyroidectomy, total thyroidectomy, and total thyroidectomy with modified neck dissection were discussed in detail with the patients.

The following data were recorded from all patients: age, sex, family history of thyroid cancer, and previous history of irradiation.

The preoperative laboratory tests included thyroid function test (free T3, free T4, and thyroid-stimulating hormone) and serum calcium. Preoperative workup included neck ultrasound with analysis of the following data: nodule size, echogenicity, calcification, vascularity, shape, and margins. It also assessed the presence of cervical lymphadenopathy with analysis of the following data: lymph node size, echogenicity, calcification, color Doppler, and shape.

Fine needle aspiration cytology (FNAC) was done in all patients, and its results were analyzed using the Bethesda system for reporting thyroid cytopathology (Table 1). Workup included also chest radiography, ECG, and indirect laryngoscopy.

Table 1 Bethesda system for reporting thyroid cytopathology

BI	Nondiagnostic or unsatisfactory
BII	Benign
BIII	Atypical or follicular lesion with undetermined significance
BIV	Follicular neoplasm
BV	Suspicious of malignancy
BVI	Malignant

Table 2 Demographic data

	Mean	SD (range) or %
Age	36.96	11.1 (19–55)
Sex		
Male	19	22.9
Female	64	77.1
Thyroid function test		
Euthyroid	78	94.0
Hypothyroidism	2	2.4
Hyperthyroidism	3	3.6

Operative

A total of 83 patients underwent surgery for STN, and type was decided depending on several factors, including patient history, ultrasound finding, presence of suspicious lymph nodes, preoperative FNAC, and patient counseling.

Hemithyroidectomy was done in benign nodules as reported by FNAC Bethesda II. A total of 35 patients underwent hemithyroidectomy, and in only one case where postoperative histopathology was reported as malignant in the paraffin section, completion thyroidectomy of the remaining lobe was done. Total thyroidectomy was done in those cases where FNAC was reported as Bethesda III–VI. In total, 40 patients underwent total thyroidectomy. Total thyroidectomy with neck dissection was done in those cases with either palpable lymph nodes in the neck or ultrasonic finding suggestive of lymphadenopathy. Only eight patients underwent total thyroidectomy with neck dissection.

Statistical analysis

Continuous variables are expressed as mean and SD. Categorical variables are expressed as frequencies and percentages. Student's *t*-test was used to assess the statistical significance of the difference between two

Table 3 Preoperative neck ultrasound findings

	n (%)
Nodule size	
<2	19 (22.9)
2–4	41 (49.4)
>4	23 (27.7)
Nodule echogenicity	
Hypoechoic	31 (37.3)
Isoechoic	21 (25.3)
Hyperechoic	16 (19.3)
Cystic	15 (18.1)
Nodule calcification	
Microcalcifications	25 (30.1)
Coarse calcifications	8 (9.6)
Peripheral rim calcification	2 (2.4)
No calcification	48 (57.8)
Nodule color Doppler	
Intranodular vascularity	31 (37.3)
No intranodular vascularity	52 (62.7)
Nodule shape	
Taller than wider	34 (41.0)
Wider than taller	31 (37.3)
No difference	18 (21.7)
Nodule margins	
Halo and regular	29 (34.9)
No halo and regular	12 (14.5)
Halo and irregular	14 (16.9)
No halo and irregular	28 (33.7)

study group mean. χ^2-Test and Fisher's exact test were used to examine the relationship between categorical variables. A significance level of *P* less than 0.05 was used in all tests. All statistical procedures were carried out using SPSS version 20 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Results show that most patients presenting with STN were females (*n*=64, 77.1%). Mean age was 36.96±11.1 years, with a range (minimum–maximum: 19–55 years). Most of the patients (*n*=78, 94%) were euthyroid, three patients were hyperthyroid, and only two patients were hypothyroid (Table 2). The most common presentation of the patients is swelling in the anterior aspect of the neck discovered accidently, and other symptoms included pain, hoarseness, and dysphagia.

The preoperative radiological and pathological assessment findings were presented in Tables 3–5. It shows regarding the preoperative ultrasound that the most important factors to be included in the ultrasound are the nodule size, which was divided into three groups less than 2, 2–4, and greater than 4 cm. The echogenicity is divided into solid and cystic, and the solid is furtherly divided into hyperechoic, isoechoic and hypoechoic lesions. Calcification, which is present in less than 50% of cases, included microcalcifications, coarse calcifications, and peripheral rim calcification. Moreover, an important factor is the nodule vascularity. Other factors include nodule shape and margins Table 3.

Regarding the lymph nodes, the size, echogenicity, calcification, vascularity, and shape were recorded (Table 4). Moreover, the results of preoperative FNAC are shown in Table 5.

Table 4 Preoperative assessment of lymph nodes

	N (%)
Lymph node size	
<8 mm	49 (59.0)
>8 mm	34 (41.0)
Lymph node echogenicity	
Solid	51 (61.4)
Cystic	32 (38.6)
Lymph node calcification	
Microcalcification	40 (48.2)
No microcalcification	43 (51.8)
Lymph node color Doppler	
Increase color Doppler flow	27 (32.5)
No increase color Doppler flow	56 (67.5)
Lymph node shape	
Loss of normal fatty hilum	35 (42.2)
No loss of normal fatty hilum	48 (57.8)

Table 5 Preoperative FNAC results

	n (%)
FNAC	
BI	2 (2.4)
BII	6 (7.2)
BIII	19 (22.9)
BIV	27 (32.5)
BV	23 (27.7)
BVI	6 (7.2)

FNAC, fine needle aspiration cytology.

Discussion

STNs are defined clinically as a localized thyroid enlargement with an apparently normal adjacent gland. According to literature, STN has a higher

Table 7 The final pathology

	n (%)
Final pathology	
Nodular goiter	45 (54.2)
Hashimoto thyroiditis	5 (6.0)
Follicular carcinoma	6 (7.2)
Papillary carcinoma	24 (28.9)
Medullary carcinoma	3 (3.6)

Table 6 Analysis of demographic data and thyroid function between types of pathology groups

	Type of pathology					
	Benign		Malignancy			
	Mean/*N*	SD/%	Mean/*N*	SD/%	*P* value	Significance
Age	35.02	11.06	39.91	10.66	*t*=0.049	Significance
Sex						
Male	5	26.3	14	73.7	χ^2=0.001	Significance
Female	45	70.3	19	29.7		
Thyroid function test						
Euthyroid	45	57.7	33	42.3	Fisher's exact test=0.279	NS
Hypothyroidism	2	100.0	0	0.0		
Hyperthyroidism	3	100.0	0	0.0		

Table 8 Analysis of thyroid scan findings between types of pathology groups

	Type of pathology [*n* (%)]		*P* value (χ^2)	Significance
	Benign	Malignancy		
Nodule size				
<2 cm	12 (63.2)	7 (36.8)	0.941	NS
2–4 cm	24 (58.5)	17 (41.5)		
>4 cm	14 (60.9)	9 (39.1)		
Nodule echogenicity				
Hypoechoic	10 (32.3)	21 (67.7)	0.001	S
Isoechoic	15 (71.4)	6 (28.6)		
Hyperechoic	12 (75.0)	4 (25.0)		
Cystic	13 (86.7)	2 (13.3)		
Nodule calcification				
Microcalcifications	8 (32.0)	17 (68.0)	0.002[F]	S
Coarse calcifications	7 (87.5)	1 (12.5)		
Peripheral rim calcification	1 (50.0)	1 (50.0)		
No calcification	34 (70.8)	14 (29.2)		
Nodule color Doppler				
Intranodular vascularity	10 (32.3)	21 (67.7)	<0.001	HS
No intranodular vascularity	40 (76.9)	12 (23.1)		
Nodule shape				
Taller than wider	14 (41.2)	20 (58.8)	0.013	S
Wider than taller	23 (74.2)	8 (25.8)		
No difference	13 (72.2)	5 (27.8)		
Nodule margins				
Halo and regular	28 (96.6)	1 (3.4)	<0.001	HS
No halo and regular	9 (75.0)	3 (25.0)		
Halo and irregular	9 (64.3)	5 (35.7)		
No halo and irregular	4 (14.3)	24 (85.7)		

HS, highly significant; S, significant. [F]Fisher's exact test of significance.

Table 9 Analysis of lymph node findings between types of pathology groups

	Type of pathology [*n* (%)]		*P* value (χ^2)	Significance
	Benign	Malignancy		
Lymph node size				
<8 mm	37 (75.5)	12 (24.5)	0.001	S
>8 mm	13 (38.2)	21 (61.8)		
Lymph node echogenicity				
Solid	46 (90.2)	5 (9.8)	<0.001	HS
Cystic	4 (12.5)	28 (87.5)		
Lymph node calcification				
Microcalcification	14 (35.0)	26 (65.0)	<0.001	HS
No microcalcification	36 (83.7)	7 (16.3)		
Lymph node color Doppler				
Increase color Doppler flow	4 (14.8)	23 (85.2)	<0.001	HS
No increase color Doppler flow	46 (82.1)	10 (17.9)		
Lymph node shape				
Loss of normal fatty hilum	5 (14.3)	30 (85.7)	<0.001	HS
No loss of normal fatty hilum	45 (93.8)	3 (6.3)		

HS, highly significant; S, significant.

risk of malignancy than multiple nodules [2]. Because of this reason, surgeons tend to treat them with high degree of suspicion and plan treatment in a systematic manner. Clinically, STNs are common, being present in up to 50% of the elderly population. Most STNs are malignant [2,5,7].

In our study, the rate of malignancy was 39.8% (*n*=33). There was a higher incidence of malignancy in males (*n*=14/19 male, 73.7%), although most presenting patients were females, the rate of malignancy in females was 29.7% (*n*=19/64 female). On analyzing the age, there was a significant

Table 10 Operative time

Benign																			
	Operation																		
		Hemithyoridectomy							Totalthyroidectomy										
		Mean	sd	Min	Max				Mean	sd	Min	Max							
Operative Time		43.94	7.84	35.0	55.00				75.06	8.60	60.0	93.0							
Malignancy																			
	Operation																		
		Hemithyoridectomy					Totalthyroidectomy						Total thyroidectomy + MND						
		Mean	sd	Min	Max		Mean	sd	Min	Max			Mean	sd	Min	Max			
Operative Time		43.00	.	43.0	43.00		73.67	9.95	60	95			132.25	12.59	117.0	150.0			
																	P	Sig	
	Operation																		
		Benign total thyroidectomy							Malignant total thyroidectomy										
		Mean	±SD	Min	Max				Mean	±SD	Min	Max					0.64	NS	
Operative Time		75.06	8.60	60.0	93.0				73.67	9.95	60	95							

difference in the mean age between benign (35.02) and malignant (39.91) groups. All malignant patients were euthyroid.

On comparing our results with the literature, we found this high incidence of malignancy reported in our study (39.8%) is mostly similar to that of Tai *et al.* [2] and Jena *et al.* [3] who reported the rate of malignancy in STNs as 33.6 and 39.7%, respectively. However, several authors reported that the detection of malignancy did not correlate with patients' sex [8–10]. Tai *et al.* [2] and Jena *et al.* [3] reported that the rate of malignancy was higher in males, and not only that, Tai *et al.* [2] stated that male sex is an independent predictor of malignancy, which is in accordance with our study and other studies as well [11,12].

Tables 6 and 7 show the final pathology of the patients, which shows that most of the malignant patients were papillary (n=24, 72.7%) with follicular rate (n=6, 18.18%), and most of the benign patients had nodular goiter (n=45, 90%). These results are in accordance with Jaheen and Sakr [6], as they reported that the rate of papillary carcinoma in STN is 72.5% and follicular carcinoma rate is 17.2%.The US findings showed that the size of the nodules does not indicate malignancy and one can find benign large STNs. It also shows that the most important US

Table 11 Age groups

	Type of pathology [n (%)]		P	Significance
	Benign	Malignancy		
Age group				
<25	9 (18.0)	4 (12.1)	0.109	NS
25–35	21 (42.0)	7 (21.2)		
35–45	9 (18.0)	8 (24.2)		
>45	11 (22.0)	14 (42.4)		

Table 12 Accuracy of Bethesda system

	Type of pathology [n (%)]	
	Benign count	Malignancy count
FNAC		
<BIV	27 (54.0)	0 (0.0)
≥BIV	23 (46.0)	33 (100.0)

Table 13 Age and Sex as single predicator factors

	Odds ratio	P	Significance	95% CI* for odds ratio	
				Lower	Upper
Age	1.030	0.188	NS	0.986	1.077
Male sex	5.796	0.003	HS	1.794	18.727

CI, confidence interval; HS, highly significant.

Table 14 Ultrasound predictors and finding

	Odds ratio	*P*	Significance	95% CI* for odds ratio	
				Lower	Upper
Hypoechoic	4.982	0.047	S	1.025	24.216
Microcalcifications	9.189	0.023	S	1.364	61.921
Intranodular vascularity by color Doppler	5.087	0.067	NS	0.892	29.006
Taller than wider shape	10.091	0.011	S	1.691	60.228
No halo and irregular margin	71.301	0.000	HS	8.567	593.436

CI, confidence interval; HS, highly significant; S, significance.

findings include the increased vascularity and the irregular nodule margins, and to a lesser extent the microcalcification, hypoechoic nodule echogenicity, and being taller than wider. Similar results were reported by other studies that investigated the ultrasound findings and the risk of malignancy in STN [13,14] (Table 8).

Table 9 shows the lymph node characteristics that predict malignancy, as it indicated the suspicious lymph nodes as follows: larger than 8 mm, cystic echogenicity, presences of microcalcification, increased vascularity, and loss of normal fatty hilum.

Table 10 shows the operative time of different benign and malignant patients who underwent hemithyroidectomy, total thyroidectomy, and total thyroidectomy with neck dissection. It shows significant increase in the time of operation in total thyroidectomy with neck dissection with mean operative time ~132 min. By comparing the operative time of total thyroidectomy in being and malignant cases, there was no significant difference.

Table 11 shows the different age groups of benign and malignant patients who underwent different types of surgeries. We divided the age groups into four groups, which is less than 25 year, 25–35 years, 36–45 years, and greater than 45 years, and the results showed that there is no age group at higher risk than the others, and the difference was not highly significant among age groups, but this needs further investigation and larger number of patients to be accurate.

Table 12 shows the comparison between the results of preoperative FNAC and the postoperative final pathology, which shows that all results if less than BIV were benign and it did not have any false-positive results, whereas greater than or equal to BIV results were benign as well as malignant cases, and all malignant cases were included in greater than or equal to BIV. Moreover, this means that its sensitivity is 100% (no false negative cases), whereas its specificity is 54% (high false-positive cases).

By studying the age and sex as single predictor factors of malignancy, it was found the that the being a male patient is highly significant single intendent factor (P=0.003), but no significant effect of age was found, as shown in Tables 13 and 14.

Moreover, by using multivariate regression to study independent factors in the thyroid nodule predicting malignancy, it was found that the strongest independent factor in our study was the 'No halo and irregular Margin' in U/S, and that microcalcifications, hypoechoic, and taller nodules were highly suspicious factors for malignancy.

Conclusion

Our study results show high incidence of malignancy within clinically detected STN and the presence of the following factors increases the incidence of malignancy: microcalcification, ultrasonography showing solid echogenicity, and lymphadenopathy detected either clinically or by U/S. Therefore, we highly recommend treating STN with high degree of suspicion, and the patient should undergo further investigations by U/S and FNAC.

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Conflicts of interest

There are no conflicts of interest.

References

1 Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, *et al.* American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J Endocrinol Invest 2010; 33:51–56.

2 Tai JD, Yang JL, Wu SC, Wang BW, Chang CJ. Risk factors for malignancy in patients with solitary thyroid nodules and their impact on the management. J Cancer Res Ther 2012; 8:379–383.

3 Jena A, Patnayak R, Prakash J, Sachan A, Suresh V, Lakshmi AY. Malignancy in solitary thyroid nodule: A clinicoradiopathological evaluation. Indian J Endocrinol Metab 2015; 19:498–503.

4 Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. J Indian Med Assoc 2009; 107:72–77.

5 Iqbal M, Mehmood Z, Rasul S, Inamullah H, Shah SS, Bokhari I. Carcinoma thyroid in multi and uninodular goiter. J Coll Physicians Surg Pak 2010; 20:310–312.

6 Jaheen H, Sakr M. Predictors of malignancy in patients with solitary and multiple thyroid nodules. J Surg 2016; 12:105–110.

7 Gupta M, Gupta S, Gupta VB. Correlation of fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. J Thyroid Res 2010; 2010:379051.

8 Salmaslioglu A, Erbil Y, Dural C, Issever H, Kapran Y, *et al.* Predictive value of sonographic features in preoperative evaluation of malignant thyroid nodules in a multinodular goiter. World J Surg 2008; 32:1948–1954.

9 Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, *et al.* Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ J Surg 2006; 76:123–126.

10 Lee SH, Baek JS, Lee JY, Lim JA, Cho SY, *et al.* Predictive factors of malignancy in thyroid nodules with a cytological diagnosis of follicular neoplasm. Endocr Pathol 2013; 24:177–183.

11 Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, *et al.* Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006; 91:3411–3417.

12 Pinchot SN, Al-Wagih H, Schaefer S, Sippel R, Chen H, *et al.* Accuracy of fine-needle aspiration biopsy for predicting neoplasm or carcinoma in thyroid nodules 4 cm or larger. Arch Surg 2009; 144:649–655.

13 Hoang JK, Lee WK, Lee M, Johnson D, Farrell S, *et al.* US Features of thyroid malignancy: pearls and pitfalls. Radiographics 2007; 27:847–860.

14 Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, *et al.* Benign and malignant thyroid nodules: US differentiation – multicenter retrospective study. Radiology 2008; 247:762–770.