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Original Article

Predictors of Malignancy in Thyroid Nodules

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ABSTRACT

Background: Better and early prediction of malignant thyroid nodule, and sure differentiation from benign one, is crucial need to decrease the rate of non-indicated surgeries.

The aim of the work: To find risk factors and predictors of malignancy in patients with thyroid nodule[s].

Patients and Methods: Fifty patients with thyroid nodule[s] were included. All patients were evaluated by history taking, clinical examination and laboratory investigations. Imaging studies included thyroid ultrasound [US]. All were also submitted to fine needle aspiration cytology [FNAC] before treatment by total or subtotal thyroidectomy. Excised tissues were sent to histopathological analysis.

Results: The incidence of malignancy was 22.0%. both benign and malignant groups were comparable as patient characteristics, complaints except the significant increase in cosmetic disfigurement among patients with benign nodules [92.3% vs. 45.5%]. Patients with malignant nodules had a significant increase of ill-defined margins, intranodular vascularity and enlarged lymph nodes [72.7%, 63.6% and 72.7% vs 5.1%, 12.8% and 25.6% respectively]. Ill-defined margins, enlarged lymph node and high grade in FNAC were the predictors of thyroid malignancy.

Conclusion: Predictors of malignant thyroid nodules are ill- defined edges, enlarged lymph node and high grade in FNAC. This helps clinicians to spare more benign cases from surgical interference.

Keywords: Thyroid; Malignant; Benign; Ultrasound; Predictor

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Thyroid nodules are found in 4% to 8% by palpation and in 10% to 41% by ultrasound study [1]. Thyroid cancer is more common than all other endocrine cancers with increasing incidence worldwide [2].

The most prevalent types of thyroid malignancies are differentiated types, papillary and follicular malignancies [3].

Clinically there are simple characteristics that are known to be risky regarding malignancy including; male sex, age below 30 years and above 60 years, family history of previous thyroid malignancy, previous exposure to neck irradiation and a hard nodule that may cause compression symptoms [4].

Being a non-invasive and inexpensive tool, ultrasound became the most frequently used imaging test in evaluating the thyroid gland [5].

In addition to clinical assessment ultrasound helps to identify risky nodules with risky criteria like micro-calcifications, hypoechogenicity, ill-defined edged nodules and solid pattern [6].

Fine needle aspiration biopsy [FNAB] is considered as the gold standard for the diagnosis of thyroid malignancy, but unfortunately about 25% of its biopsies are non-diagnostic [7].

More recently, Thyroid stimulating hormone [TSH] is considered as a predictor of malignancy in thyroid nodules in many studies. There is a relationship between TSH and malignancy as the TSH promotes thyroid cell proliferation through cyclic AMP [8].

Irrespective of all these developments, there is still a debate about the ideal approaches and actual predictors of malignant thyroid nodules. Thus, the current study had been designed.

AIM OF THE WORK

The aim of this study is to find risk factors and predictors of malignancy in patients with thyroid nodule[s].

PATIENTS AND METHODS

This was a prospective study carried out at the Department of Surgery, Damietta Faculty of Medicine, Al-Azhar University, Egypt. It included 50 patients with thyroid nodule[s] from November 2019 to June 2020. The study protocol was approved by the Local Ethics and Research Committee. In addition, an informed consent was signed by every patient after full clarification of study protocol. Patients' privacy and rights were assured.

The exclusion criteria were: patients with previous thyroid surgery for thyroid cancer, patients with previous cervical nodal biopsy, patients whose FNAC was established as malignant.

All patients with thyroid nodules were evaluated by detailed history taking [patient demographics, main complaint, past and family history, the duration of disease, etc…] and clinical assessment. In addition, laboratory tests including Thyroid stimulating hormone [TSH], Tri-iodo-thyronin [Free T3] and Thyroxin [Free T4].

Imaging studies included thyroid ultrasound [US], and for each nodule the following criteria were evaluated [number, maximum diameter of the nodule, calcifications [micro or macro-calcification], echo-genicity, margins [ill-defined or well defined], consistency [solid, cystic, mixed] and vascularity]. In addition, suspicious lymph nodes were evaluated.

The criteria by which a cervical LN was considered suspicious were: size >0.5 cm, shape [rounded, not oval], hilum [lost hilum, replaced fatty hilum], irregular margins, heterogeneous echo-texture, cystic degeneration of LN, calcification, vascularity throughout the periphery of LN instead of normal central hilar vessels by Doppler [9].

Micro-calcifications were defined as round laminar crystalline calcific spots < 1 mm [10-100 Um] without acoustic shadowing. However, macrocalcifications were defined as large irregularly shaped dystrophic calcifications more than 1mm, with posterior acoustic shadowing [10].

Finally, computed tomography was carried out to detect retrosternal extension of the thyroid gland for

those patients in whom US neck couldn't detect the inferior border on the gland, evaluate the local extension in more advanced stages of thyroid cancer, and it is appropriate for a suspicious mass with bulky cervical lymph nodes. In addition, all patients submitted to fine needle aspiration cytology [FNAC] before treatment by total, subtotal or hemi-thyroidectomy. The cytological specimens were examined and classified according to the Bethesda classification [11].

Intraoperatively, patients were assessed for risk factors for thyroid cancer [such as worrisome metastatic lymph nodes, local invasion suggesting extrathyroidal extension [ETE], criteria of local structures invasion and metastatic lymph nodes confirmed on intraoperative frozen section analysis.

Statistical Analysis: Data were analyzed using statistical package for social science [SPSS] software computer program, version 18 [SPSS Inc., Chicago, Illinois, USA]. Data were described using mean and standard deviation [SD] and frequencies according to the type of data [quantitative or categorical respectively]. Chi square test was used for comparison of qualitative variables. Multivariate regression analysis had been performed after single analysis to detect predictor factors.

RESULTS

The incidence of malignancy in the current study was 22.0% [11 patients]. Patient age ranged between 17 and 70 years, the average age [SD] was 40.91±11.67 years. Both benign and malignant subgroups were comparable as regard to the patient age group, patient gender, complaints except cosmetic disfigurement which is significantly higher among benign when compared to malignant subgroups [92.3% vs 45.5%], a history of radiation exposure, positive family history and smoking habit [Table 1].

TSH ranged between 0.01 to 18.0mIU/liter and there was no significant difference between patients with malignant or benign thyroid nodules [Table 2].

In the current work, patients with benign when compared to malignant thyroid nodules revealed non-significant differences regarding to the number of nodules, consistency, echogenicity, calcification or size. On the other side, patients with malignant nodules had a significant increase in ill-defined margin, intranodular vascularity and enlarged lymph nodes [72.7%, 63.6% and 72.7% vs 5.1%, 12.8% and 25.6% respectively] [Table 3].

The results of the FNAC revealed that, patients with malignant thyroid nodules had significantly higher grade of Bethesda grade when compared to patients with benign nodules [no any patients in malignant group had grades I or II, while 9.1%, 18.2%, 18.2% and 54.5% had grades III, IV, V and VI; while in benign group, the majority were grades I and II [5.1% and 74.4% respectively], 15.4% were grade III, 2.6% were grade IV and only 2.6% were grade VI [Table 4].

In the current work, ill-defined margins, enlarged lymph node and high grade in FNAC were the predictors of thyroid malignancy [Table 5].

Table [1]: Patient characteristics, chief complaints, past and family history among studied patients

Variables		Benign [39; 78%]	Malignant [11; 22%]	Test	P value
Age group [year]	<30	5[12.8%]	1[9.1%]	8.55	0.07
	30-40	24[61.5%]	4[36.4%]		
	41-50	7[17.9%]	3[27.3%]		
	51-60	3[7.7%]	1[9.1%]		
	>60	0[0.0%]	2[18.2%]		
Sex	Male	6[15.4%]	3[27.3%]	0.82	0.36
	Female	33[84.6%]	8[72.7%]		
Complaints	Cosmetic disfigurement	36 [92.3%]	5[45.5%]	**12.76**	**0.002***
	Dyspnea	0[0.0%]	1[9.1%]	3.61	0.22
	Dysphagia	1 [2.6%]	2[18.2%]	3.71	0.11
	Voice hoarseness	0[0.0%]	0[0.0%]	a	
History of irradiation exposure		1 [2.6%]	1[9.1%]	0.95	0.32
Positive family history		0[0.0%]	1[9.1%]	3.61	0.22
Smoking		1 [2.6%]	1[9.1%]	0.95	0.32

Table [2]: Serum levels of thyroid stimulating hormone [TSH] among studied groups

	N	Mean	S. D	Minimum	Maximum	t	p
Benign	39	1.6421	2.43910	0.01	14.00	0.16	0.447
Malignant	11	2.4282	5.19782	0.01	18.00		
Total	50	1.8150	3.19932	0.01	18.00		

Table [3]: Ultrasound findings among studied populations

Variables		Benign [39]	Malignant [11]	Test	P value
Number of nodules	Single	15 [38.5%]	7[63.6%]	2.20	0.12
	Multiple	24 [61.5%]	4[36.4%]		
Consistency	Solid	12 [30.8%]	7[63.6%]	3.95	0.13
	Cystic	8[20.5%]	1[9.1%]		
	Mixed	19[48.7%]	3[27.3%]		
Echogenicity	Hypo	20 [51.3%]	9[81.8%]	3.53	0.17
	Hyper	5[12.8%]	1[9.1%]		
	Iso	14[35.9%]	1[9.1%]		
Margins	Well-defined	37 [94.9%]	3[27.3%]	24.50	<0.001*
	Ill-defined	2[5.1%]	8[72.7%]		
Calcification	Macro	29[74.4%]	6[54.5%]	1.60	0.21
	Micro	10[25.6%]	5[45.5%]		
Intra-nodular vascularity	Present	5[12.8%]	7[63.6%]	12.14	0.002*
	Absent	34 [87.2%]	4[36.4%]		
Size	≤ 2cm	12[30.8%]	6[54.5%]	2.10	0.14
	>2cm	27[59.2%]	5[45.5%]		
Enlarged LNs		10[25.6%]	8[72.7%]	8.25	0.004*

Table [4]: Fine needle aspiration cytology

Bethesda grade	Benign		Malignant		X2	p
	n.	%	n.	%		
I	2	5.1%	0	0.0%	36.12	<0.001*
II	29	74.4%	0	0.0%		
III	6	15.4%	1	9.1%		
IV	1	2.6%	2	18.2%		
V	0	0.0%	2	18.2%		
VI	1	2.6%	6	54.5%		

Table [5]: Multivariate analysis of predictors of thyroid malignancy in studied patients

Predictors of Malignancy	B	SE	P Value	95.0%CL	
				Lower	Upper
Ill-defined Margins	0.25	0.11	0.029*	0.027	0.48
Vascularity	0.006	0.091	0.95	-0.17	0.18
Enlarged lymph node	-0.24	0.06	0.002*	-0.33	-0.084
FNAC	0.62	0.026	<0.001*	0.12	0.22

DISCUSSION

Thyroid nodules are a common clinical problem, with prevalence rate of 5.0% of females and 1.0% of males living in iodine-sufficient countries. Prediction of malignant nodules is a critical issue and the development of ultrasound adds to the field a non-invasive modality. However, its value and predictive parameters are questioned [12]. The current work is an effort to identify predicting variables [clinical, intraoperative or radiological], fine needle aspiration cytology in the identification of malignant thyroid nodules.

Results revealed that, patients with benign nodules complained more significantly than those with malignant nodules of cosmetic disfigurement [92.3% vs 45.5%]. However, these percentages recognized

disfigurement as the most common complaint. Otherwise, patients with malignant nodules had a significant increase in ill-defined margin on ultrasound examination, higher intranodular vascularity, more enlarged lymph nodes and higher grades on Bethesda classification. However, running multiple logistic regression revealed that, ill-defined margins, enlarged lymph nodes and results of FNAC [high grade] were the predictors of malignant nodules.

For the final diagnosis of malignancy, the histo-pathological examination was used as the gold-standard in the current work, although previous studies considered FNAC as the gold standard for the diagnosis of most thyroid nodules [13,14]. However, FNAC had a failure rate of extending between 30% and 70.0% [15].

This high failure rate could be attributed to coarse [macro] or micro-calcification especially with thick-walls of thyroid nodules makes the penetration of this wall very difficult and even penetration achieved the enough sample for cytology is hard to be obtained [13-14].

The incidence of malignant nodules in the current work is 22.0% which is higher than the previously reported value by Alexander *et al*. [16] [incidence rate 5-15%].

The incidence rate of thyroid nodules is increasing due to the introduction of new methods of diagnosis [i.e, wide use of ultrasound]. However, minority of nodules require surgery [17].

Cozzolino *et al*. [18] reported a high incidence of malignant nodules reaching 38.5%. This heterogeneity in the incidence of malignancy was attributed to different selection criteria.

In the current work, malignant nodules were more common among males than females and in older than younger patients. However, the difference was statistically non-significant.

This is comparable to results of Al-Hakami *et al*. [19] who reported that, thyroid malignancy was more prevalent in males than females, and in patients who were older than or equal to 45 years [but with significant difference].

Similar results to the current study were reported by Witczak *et al*. [20] who reported non-significant difference between benign and malignant nodules regarding patient's age or gender. However, Paul *et al*. [10] reported a significant increase of malignancy among females, which is contradictory to the current study and could be attributed to different inclusion criteria and sample size. In addition, geographic differences could explain this contradiction.

In the current work, both benign and malignant groups had no difference regarding family history of thyroid cancer. However, previous studies had reported that, positive family history is one of the known clinical risk factors for the development of malignant nodules [12, 21]. However, and similar to the current study, Cozzolino *et al*. [18] found that, positive family history is not associated with the risk of thyroid malignancy.

No significant difference could be detected regarding the previous exposure to radiation. Pellegriti *et al*. [22] reported that exposure to radiation is the most likely contributing factor to cancer thyroid but also other environmental carcinogens can contribute.

The single nodule was increased among malignant when compared to benign nodules [63.6% vs 38.5% respectively]. However, the difference was statistically non-significant. Frates *et al*. [6] reported that a solitary nodule is associated with higher risk of malignancy than multiple nodules [p <0.01].

In addition, Li JZ *et al*. [23] reported that the incidence of thyroid cancer in higher among patients a single nodule. However, Gandolfi *et al*. [24] reported that multiple nodules should no longer be considered an indicator of benign disease and should be assessed as a solitary nodule.

On the other side, El-Gammal *et al*. [25] reported that multiple nodules were significantly associated with malignancy than solitary nodules.

In the current study, small nodule size less than 2cm was more common among malignant nodules. However, the difference is not statistically significant. This is comparable to Albuja-Cruz *et al*. [26] who reported non-significant association between nodule size and risk of malignancy.

Moreover, Megwalu *et al*. [27] reported similar results denying the association between tumor size and risk of malignancy.

In the current work, the only predictors of malignant nodules were ill defined margins, enlarged lymph node and high grade in FNAC.

These results agree with Jinih *et al*. [28] who reported that, their results suggested that, nodule size is not accurately predict the risk of thyroid malignancy irrespective of the results of FNAC.

Results of the current work also in agreement with Cozzolino *et al*. [18] who reported that, although nodular vascularity was more frequent in malignant nodules at univariate analysis, it was not a factor to predict thyroid malignancy at multivariate analysis.

However, there study contradict the current one in the defined predictors of malignancy as they only found a small tumor size and microcalcification are the predictors of malignant nodules. The fact that, they restricted their study to specific populations with specific criteria of thyroid nodules [grey zone; intermediate cytopathology thyroid nodules] could explain this contradiction.

The value of vascularization in the evaluation of thyroid malignant nodules has been much debated [29].

Brunese *et al*. [30] argued that intralesional vascularity raises the suspicion of malignancy, while Frates *et al*. [6] demonstrate that intralesional vascularity not has a role.

Jaheen and Sakr [31] reported that micro-calcifications are a significant risk factor of malignancy. This could be recognized in the current study too.

Paul *et al*. [10] reported that ill-defined edges suggest malignant infiltration of adjacent thyroid parenchyma with no pseudo capsule formation.

Jaheen and Sakr [31] also reported that ill-defined edges are a significant predictor of malignancy with a significant predictive value [p=0.029]. Another study by Witczak *et al*. [20] reported similar results. These results are confirmed in the current study.

In the current work, echogenicity could not differentiate between benign and malignant nodules and could not predict malignant transformation.

Kapali *et al*. [32] reported that the sensitivity of hypo-echogenicity in predicting malignancy was 84%.

On the other hand, another trial found that hypo-echoic pattern is not significant in predicting malignancy by Jaheen and Sakr [31] as in the current study.

Solid consistency could not be found to predict malignant thyroid.

This is agreeing with Macias *et al*. [33] who reported that the solid nature of the thyroid nodule is not a significant predictor of malignancy.

In agreement with the current work, Kapali *et al*. [32] reported that, enlarged lymph nodes are predictors of malignancy in thyroid nodules, and similar results were reported by Jaheen and Sakr [31], while Paul *et al*. [10] reported that, enlarged lymph nodes are of low value in predicting malignancy in thyroid nodules.

It is clearly evident that there was a gradual increase in incidence of malignancy from with increased Bethesda grade, with the highest incidence in grade six, making higher grades significant in prediction of malignancy in thyroid nodules.

Conclusion:

There are significant predictors of malignancy in thyroid nodules such as ill- defined edges, enlarged lymph node and high grade in FNAC. This helps clinicians to spare more benign cases from surgical interference. However, the small number of included patients represent a limitation of the current work, and future larger scale trials are required.

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None

REFERENCES

1. Sharma G, keshava G, Hanchinal V. Ultrasonographic Evaluation of Thyroid Nodules with Pathologic Correlation. International journal of anatomy, radiology and surgery.2016.doi: 10.7860/ IJARS/ 2016/ 23868:222.32.
2. Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing? Curr Opin Oncol. 2015;27[1]:1-7. doi: 10. 1097/CCO.0000000000000 148.
3. Townsend CM, Evers BM, Beauchamp RD, Mattox KL. Sabiston textbook of surgery 20th [edn]: Canada/ Elsevier; 2017. p.881-940.
4. Hegedüs L. Clinical practice. The thyroid nodule. N Engl J Med. 2004; 351[17]:1764-71. doi: 10.1056/NEJMcp 031436.
5. Nachiappan AC, Metwalli ZA, Hailey BS, Patel RA, Ostrowski ML, Wynne DM. The thyroid: review of imaging features and biopsy techniques with radiologic-pathologic correlation. Radiographics. 2014 Mar-Apr;34[2]:276-93. doi: 10.1148/ rg.342135067.
6. Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab. 2006;91[9]:3411-7. doi: 10. 1210/jc. 2006-0690.
7. Coorough N, Hudak K, Jaume JC, Buehler D, Selvaggi S, Rivas J, Sippel R, Chen H. Nondiagnostic fine-needle aspirations of the thyroid: is the risk of malignancy higher? J Surg Res. 2013 Oct;184[2]:746-50. doi: 10.1016/j.jss. 2013.02.018.
8. Li H, Li X, Liu J, Jin L, Yang F, Wang J, Wang O, Gao Y. Correlation between serum lead and thyroid diseases: papillary thyroid carcinoma, nodular goiter, and thyroid adenoma. Int J Environ Health Res. 2017;27[5]:409-419. doi: 10.1080/09603123.2017.1373273.
9. Hoang JK, Lee WK, Lee M, Johnson D, Farrell S. US Features of thyroid malignancy: pearls and pitfalls. Radiographics. 2007;27[3]:847-60; discussion 861-5. doi: 10.1148/rg.273065038.
10. Paul P, Ali KA, Jasir M. predictors of malignancy in solitary nodule thyroid. Int Surg J. 2017; 4:703-8. doi: 10.18203/2349-2902.isj20170217
11. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2009 Nov;19 [11]: 1159-65. doi: 10.1089/thy.2009.0274.
12. Chen D, Hu J, Zhu M, Tang N, Yang Y, Feng Y. Diagnosis of thyroid nodules for ultrasonographic characteristics indicative of malignancy using random forest. BioData Min. 2020 Sep 3; 13:14. doi: 10.1186/ s13040-020-00223-w.
12. Ianni F, Campanella P, Rota CA, Prete A, Castellino L, Pontecorvi A, Corsello SM. A meta-analysis-derived proposal for a clinical, ultrasonographic, and cytological scoring system to evaluate thyroid nodules: the "CUT" score. Endocrine 2016; 52[2]:313–321. doi: 10.1007/s1202 0-015-0785-5
13. Singh Ospina N, Brito JP, Maraka S, Espinosa de Ycaza AE, Rodriguez-Gutierrez R, Gionfriddo MR, *et al*. Diagnostic accuracy of ultrasound-guided fine needle aspiration biopsy for thyroid malignancy: systematic review and meta-analysis. Endocrine 2016; 53:651–61. doi: 10.1007/s12020-016-0921-x.
14. Lee J, Lee SY, Cha SH, Cho BS, Kang MH, Lee OJ. Fine-needle aspiration of thyroid nodules with macro-calcification. Thyroid 2013; 23:1106–12.doi: 10.1089/ thy.2012.0406
15. Na DG, Kim DS, Kim SJ, Ryoo JW, Jung SL. Thyroid nodules with isolated macrocalcification: malignancy risk and diagnostic efficacy of fine-needle aspiration and core needle biopsy. Ultrasonography 2016; 35:212–9. 10.14366/usg.15074
16. Alexander EK, Marqusee E, Orcutt J, Benson CB, Frates MC, Doubilet PM, Cibas ES, Atri A. Thyroid nodule shape and prediction of malignancy. Thyroid. 2004 Nov;14[11]:953-8. doi: 10.1089/thy.2004.14.953.
17. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26[1]:1-133. doi: 10.1089/thy.2015.0020.
18. Cozzolino A, Pozza C, Pofi R, Sbardella E, Faggiano A, Isidori AM, Giannetta E, Pernazza A, Rullo E, Ascoli V, Lenzi A, Gianfrilli D. Predictors of malignancy in high-risk indeterminate [TIR3B] cytopathology thyroid nodules. J Endocrinol Invest. 2020 Aug;43[8]:1115-1123. doi: 10.1007/s40618-020-01200-0.
19. Al-Hakami HA, Alqahtani R, Alahmadi A, Almutairi D, Algarni M, Alandejani T. Thyroid Nodule Size and Prediction of Cancer: A Study at Tertiary Care Hospital

in Saudi Arabia. Cureus. 2020 Mar 30;12[3]: e7478. doi: 10.7759/cureus.7478.

20. Witczak J, Taylor P, Chai J, Amphlett B, Soukias JM, Das G, Tennant BP, Geen J, Okosieme OE. Predicting malignancy in thyroid nodules: feasibility of a predictive model integrating clinical, biochemical, and ultrasound characteristics. Thyroid Res. 2016 May 25; 9:4. doi: 10.1186/s13044-016-0033-y.

21. Campanella P, Ianni F, Rota CA, Corsello SM, Pontecorvi A. Quantification of cancer risk of each clinical and ultrasonographic suspicious feature of thyroid nodules: a systematic review and meta-analysis. Eur J Endocrinol. 2014 Apr 10;170[5]: R203-11. doi: 10.1530/EJE-13-0995.

22. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013; 2013:965212. doi: 10.1155/2013/965212.

23. Li JZ, Jin YJ, Liu X, Zhang LY. [Association between the serum TSH concentration and thyroid cancer incidence]. Zhonghua Zhong Liu Za Zhi. 2011 Dec;33 [12]: 921-4. Chinese. PMID: 22340102.

24. Gandolfi PP, Frisina A, Raffa M, Renda F, Rocchetti O, Ruggeri C, Tombolini A. The incidence of thyroid carcinoma in multinodular goiter: retrospective analysis. Acta Biomed. 2004 Aug;75[2]:114-7. PMID: 15481700.

25. El-Gammal A, E-Balshy MA, Zahran KM. Relationship between thyroid nodule size and incidence of thyroid cancer. Menoufia Med J. 2019, 32:1142-1148. doi: 10.4103/mmj.mmj_178_18

26. Albuja-Cruz MB, Goldfarb M, Gondek S, Allan BJ, Lew JI: Reliability of fine-needle aspiration for thyroid nodules greater than or equal to 4 cm. J Surg Res. 2013; 181:6-10. doi: 10.1016/j.jss.2012.06.030

27. Megwalu UC. Risk of malignancy in thyroid nodules 4 cm or larger. Endocrinol Metab. 2017, 32:77-82. doi: 10.3803/EnM.2017.32.1.77

28. Jinih M, Faisal F, Abdalla K, Majeed M, Achakzai AA, Heffron C, McCarthy J, Redmond HP. Association between thyroid nodule size and malignancy rate. Ann R Coll Surg Engl. 2020 Jan;102[1]:43-48. doi: 10.1308/rcsann.2019.0156.

29. Rago T, Vitti P. Diagnostic role of ultrasound and elastosonography in nodular goiter. Best practice and research. Clin Endocrinol Metabol. 2014; 28[4]:519–529. doi: 10.1016/j.beem.2014.02.003

30. Brunese L, Romeo A, Iorio S, Napolitano G, Fucili S, Biondi B, Vallone G, Sodano A. A new marker for diagnosis of thyroid papillary cancer: B-flow twinkling sign. J Ultrasound Med. 2008 Aug;27[8]:1187-94. doi: 10.7863/jum.2008.27.8.1187. PMID: 18645077.

31. Jaheen H, Sakr M. Predictors of Malignancy in Patients with Solitary and Multiple Thyroid Nodules. Journal of Surgery [Jurnalul de chirurgie]. 2016; 12[3]:105-110.

32. Kapali A, Jaipal B R, Raghuram P, Ravindra Bangar, Sateesh Kumar Atmakuri. Role of ultrasonography in thyroid nodules with pathological correlation. Int J Contemporary Med Res. 2016; 3[5]:1451-1453.

33. Macias CA, Arumugam D, Arlow RL, Eng OS, Lu SE, Javidian P, Davidov T, Trooskin SZ. A risk model to determine surgical treatment in patients with thyroid nodules with indeterminate cytology. Ann Surg Oncol. 2015;22[5]:1527-32. doi:10.1245/s10434-014-4190-8.

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