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Research Paper

The Role of Thyroglobulin as Predictive Biomarker for Diagnosis of Differentiated Thyroid Cancer in Al-Imammein Al-Kadhumain Medical City

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ABSTRACT:

BACKGROUND:

Several line of evidence have indicated the role serum thyroglobulin (Tg) concentrations in differentiating malignant from benign thyroid cancer. However, such a role in differentiating follicular from papillary thyroid carcinoma still needs more studies.

OBJECTIVE:

To evaluate the prognostic value of preoperative serum Tg level in differentiation between follicular and papillary thyroid cancer in patients undergoing thyroidectomy.

PATIENTS AND METHODS:

This is a retrospective single center study including 50 patients diagnosed with thyroid carcinoma and scheduled to have total thyroidectomy. Patients" demographic and final histopathology reports were obtained. Serum Tg was measure preoperative.

RESULTS:

Papillary thyroid carcinoma (PTC) was reported in 38 patients (76%), while the other 12 patients (24%) were found to have follicular thyroid carcinoma (FTC). The sensitivity and specificity of Tg in detection of PTC was 60.53% and 33.33%. While the sensitivity and specificity of Tg was 33.33% and 60.52% in predicating FTC. Hypocalcemia was the most common complication, up to 10%. There was no significant relationship between any of the included demographic or clinical factors and the type of cancer or the development of complications.

CONCLUSION:

Thyroglobulin has a moderate sensitivity for detection PTC (60.53%), while it has poor sensitivity for detection FTC (33.33%).

KEYWORDS: Follicular and papillary thyroid carcinoma, thyroglobulin, sensitivity and specificity

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INTRODUCTION:

Background Thyroid cancer is the second most common type of endocrine malignancy after breast cancer. About 90% of thyroid neoplasms are differentiated thyroid cancers (DTC) with low malignant potential and a very good prognosis [(1)].

Thyroid cancer has no established etiologic factors, although exposure to radiation has been implicate for several decades. The phenomenon of radiation exposure leading to increased incidence of thyroid cancer was documented following the atomic bomb exposure in Hiroshima and Nagasaki during World War II [(2)]. More recently, it was shown after the Chernobyl accident, which was followed by a steep rise in thyroid cancer among children exposed to the radiation fallout [(3)]. Within the past 2 decades, however, there has been a rise in the incidence of thyroid cancer during the fourth and fifth decades of life [(4)]. The increased diagnoses may be attributable to incidental findings of tumors on imaging studies, such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), performed for other reasons [(5)]. In the United States, occult thyroid cancers are reported with an incidence of approximately 10% among people who died of other causes[(6)].

Classification categorizes thyroid malignancies to two main groups [(7)]:

Differentiated and undifferentiated cancers: Differentiated thyroid cancers consisting approximately 90% of all thyroid cancers,

differentiated thyroid cancer is the most prevalent type of these cancers [8], which is raised from thyroid follicular epithelial cells. There are two main subtypes for differentiated thyroid cancers: well-differentiated and poorly differentiated thyroid cancers. Papillary thyroid cancer, follicular thyroid cancer, and (HCC) are under category of well-differentiated thyroid cancers [9].

Papillary thyroid cancer:

Constitutes approximately 70-90% of all thyroid cancer cases.

The incidence increases with age, and women are more frequently affected than men, in ratios of 2:1 to 4:1 [10].The aetiology of PTC has evoked much interest. The clinical spectrum of PTC ranges from indolent papillary thyroid microcarcinomas [11].

Follicular thyroid cancer:

Including approximately 10–15% of well-differentiated thyroid carcinomas. Some studies report the incidence of follicular thyroid cancer to be approximately 10% in iodine sufficient areas and 25 to 40% in areas of iodine deficiency [12]**.**

Hurthle cell carcinoma:

Oncocytic follicular cells of thyroid, known as Hurthle cells, which were first described by Karl Hürthle are the origin of Hurthle cell carcinoma [13]. Histologic differentiation between Hurthle cell adenoma and carcinoma can be definitely made only after the evaluation of resection specimen by the presence or absence of vascular or capsular invasion, which is the hallmark of HCC. HCC represents 3% of all thyroid cancers [14].There are two types of Hurthle cell carcinoma; minimally invasive carcinomas are fully encapsulated tumors with microscopically identifiable foci of capsular or vascular invasion (<4 foci) and widely invasive tumors, which have extensive vascular invasion (>4 foci) and extrathyroidal invasion. Patients with minimally invasive carcinomas usually experience a better prognosis. Overall, older patients and those with larger tumor size, extrathyroidal extension, and not undergoing surgery have reduced survival [15].

Diagnosis

Sonographic patterns suspicious of malignancy are microcalcifications, irregular margins, solid consistency, hypoechogenity, extrathyroidal extension and a tall shape rather than a wide one.

Intranodulary vascularization does not seem to have a clear correlation with malignancy [16]. Roughly one third of thyroid nodules are larger than 1 cm and eligible for scintigraphy [17]. The guidelines of the German Society of Nuclear Medicine recommend a scintigraphic examination of every thyroid nodule >1 cm.

Cytological analysis is performed according to the Bethesda System for Reporting Thyroid Cytopathology. The findings are graded into six categories: I: nondiagnostic/unsatisfactory; II: benign; III: atypia of undetermined significance/follicular lesion of undetermined significance; IV: follicular neoplasm/suspicious for follicular neoplasm; V: suspicious for malignancy; VI: malignant [18].

Thyroglobulin, the precursor protein for thyroid hormone synthesis is detectable in the serum of most normal individuals when a sensitive method is used. The serum Tg level integrates three major factors: (i) the mass of differentiated thyroid tissue present; (ii) any inflammation or injury to the thyroid gland which causes the release of Tg; and (iii) the amount of stimulation of the TSH receptor (by TSH, hCG or TRAb) [19]

Therapy of Differentiated Thyroid Carcinoma

DTC should be treated interdisciplinary in facilities with an appropriate expertise in order to ensure an optimal long-term treatment quality. Specialists in surgery, pathology and nuclear medicine should be available. The therapeutic approach is individualized and risk-adapted [18].

Surgery

Thyroid carcinomas >1 cm and/or for all metastasized or macroscopically invasive PTC irrespective of size, total thyroidectomy is recommended [20].If lymph node metastases have been detected sonographically or intraoperatively, lymph node dissection in the affected compartment should be done to reduce the risk of (local) recurrence. On the other hand, the main arguments against a prophylactic dissection are the lack of evidence regarding a better outcome of the patients and the remarkably higher complication rate due to the more extensive intervention (e.g., vocal cord paralysis). After all, accurate histopathological examination of the specimen after total thyroidectomy and lymphadenectomy (if done) is regarded as the gold standard and is indispensable for the management and further diagnostic and therapeutic approach [18].

AIMS OF THE STUDY:

To evaluate the prognostic value of preoperative serum Tg level in differentiation between follicular and papillary thyroid cancer in patients undergoing thyroidectomy.

PATIENT AND METHODS:

2.1.study design and setting This is a retrospective single center study including 50 patients diagnosed with thyroid carcinoma and scheduled to have total thyroidectomy by

single surgeon at the department of Surgery/ Al-Imamain Al-Kadhumain Medical City during the period from January 2020 to December 2021.

Inclusion Criteria :

Age ≥ 16 years old,total thyroidectomy,Available preoperative Tg measurements and final histopathology reports.

Exclusion Criteria : Patients < 16 years old,Patients with undifferentiated thyroid cancer.

Ethical consideration :A written consent from each participant was obtained prior to data collection after explaining the aim of study. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

Data Collection:

Collected data included patients' demographic (age, gender, final histopathology reports, and preoperative Tg measurements**.**

Biochemical Assay and Study:

GroupsBlood samples were collected from all patients after enrollment in the study. A ready commercial kit was used to measure serum level of Tg using competitive radioimmunoassay.

Histopathology

The histological study was carried out in accordance with the World Health Organization Classification of Thyroid Tumors, which helped determine the histopathological kinds of thyroid cancer.

Follow up:

After surgery, patients were followed up for 6 months. There was a regular monthly visit for outpatient's clinic of the same hospital**.**

Data Analysis:

The data were analyzed with descriptive statistics using the SPSS version 25. The mean and standard deviation of continuous variables were calculated and evaluated using the Student t-test. The Chi square was used to examine binomial variables that were expressed as frequency and percentage. Tg's diagnostic value, sensitivity, specificity, positive predictive value, and negative predictive value between PTC and FTC were calculated. A statistically significant value of P 0.05 was used.

RESULT:

Demographic Characteristics of the Patients

Mean age of the patients was 36.2±11.23 years (range 16-60 years). The age class 16-30 years was the most frequent accounting for more 44% of the patients followed by age class 31-45 years (36%). About three quarters of the patients were females.

Table 1: Patients' characteristics and demographic data (n=50).

Variables	Frequency	Percentage
Age, years		
16-30	22	(44%)
31-45	18	(36%)
46-60	10	(20%)
Gender		
Male	12	(24%)
Female	38	(76%)
Comorbidities		
No comorbidity	25	(50%)
DM	11	(22%)
HTN	10	(20%)
Others	4	(8%)
TSH, mU/L		
Mean±SD Range	1.87±1.3 0.92-3.43	------
Complications		
No complications	36	(72%)
Hypocalcemia	5	(10%)
)temporary)	4	(8%)
Hoarseness of voice	5	(10%)
Others		

DM: diabetes mellitus, HTN: hypertension. Other comorbidities include one case of asthma and one case of ischemic heart disease. Other complications include cases of dysphagia, keloid scar.

Half of the patients (50%) had no comorbidity, while 22% and 20% of them were suffering from DM and hypertension, respectively. Mean serum level of TSH was 1.87±1.3 mU/L. About three-fourths of the patients (72%) had no complication alongside the follow up period. However, 10% of the patients developed

hypocalcemia, while 8% of them had hoarseness of the voice (Table 3-1).

Histopathologic Results

PTC was reported in 38 patients (76%), while the other 12 patients (24%) were found have FTC.

Sensitivity and Specificity of Tg in Predicting Papillary Thyroid Carcinoma

Out of 38 patients having PTC according to histopathological finding, 23 was positive for Tg. On the other hand, 4 patients out of 12 patients negative for PTC according to histopathology were also found be positive for Tg. As a result, Tg's sensitivity and specificity were 60.53% and 33.33%, respectively. Tg had a positive and negative predictive value of 74.19% and 21%, respectively (Table 2).

Table (2): Sensitivity and specificity of Tg in prediction of papillary thyroid carcinoma.

		Histopathology		Total
		Positive	Negative	
Tg	Positive	23	8	31
	Negative	15	4	19
	Total	38	12	50

Sensitivity = 23/ (23+15) ×100 = 60.53%
Specificity = 4/ (4+8) ×100 = 33.33%
Positive predictive value= 23/ (23+8)× 100= 74.19%
Negative predictive value= 4/ (4+15) ×100= 21%

Sensitivity and Specificity of Tg in Predicting Follicular Thyroid Carcinoma

Out of 12 patients having FTC according to histopathological finding, only 4 was positive for Tg. On the other hand, 23 patients out of 38 patients negative for FTC according to histopathology were also found be positive for Tg. Accordingly, the sensitivity and specificity of Tg was 33.33% and 60.52% respectively. The positive and negative predictive value of Tg were 21% and 74.2%, respectively (Table 3).

Table (3): Sensitivity and specificity of Tg in prediction of follicular thyroid carcinoma

		Histopathology		Total
		Positive	Negative	
Tg	Positive	4	15	19
	Negative	8	23	31
	Total	12	38	50

Sensitivity = 4/ (4+8) ×100 = 33.33%
Specificity = 23/ (23+15) ×100 = 60.52%
Positive predictive value= 4/ (4+15)× 100= 21%
Negative predictive value= 23/ (23+8) ×100=74.2%

Association of demographic and clinical factors with thyroid malignancy

The mean age of the patients in follicular group was 39.76±12.86 years which was higher than that of papillary group (33.62±9.29 years). However, the difference was not significant. On the other hand, the HTN and DM was more common among patients with PCT than those with FCT with no significant difference. Interestingly, 60.52% of the patients with PCT were positive for Tg compared with 33.33% of patients with FCT who were positive for this marker with a significant difference (Table 4).

Table (4): Association of demographic and clinical factors with thyroid malignancy.

Variables	Follicular (n=12)	Papillary (n=38)	p-value
Age, years Mean±SD Range	 39.76±12.86 16-60	 33.62±9.29 16-50	0.058
Gender Male Female	 3(28.57%) 9(71.43%)	 9(23.68%) 29(76.32%)	0.724
Comorbidities No comorbidity DM HTN Others	 8(66.67%) 3(25%) 1(8.33%) 0(0%)	 17(44.74%) 8 (21.1%) 9(23.68%) 4(10.53%)	 0.126 0.379 0.535 0.219
TSH, mu/L ≤2 >2	 10(83.33%) 2(16.77%)	 35(92.11%) 3(7.89%)	0.631
Tg Negative Positive	 8(66.67%) 4(33.33%)	 15(39.47%) 23(60.52%)	0.044

Association of demographic and clinical factors with Complications

Generally, patients with and without complications were comparable in terms of all included demographic and clinical factors with no significant differences. Although, patients with complication had higher frequency of DM compared with those without complication, the difference was not significant (Table 5).

Table(5):Association of demographic and clinical factors with Complications .

Variables	Without complications (n=36)	With complications (n=14)	p-value
Age, years Mean±SD Range	 37.26±12.52 16-60	 34.47±8.78 22-47	0.401
Gender Male Female	 7(19.44%) 29(80.56%)	 5(35.71%) 9(64.28%)	0.128
Comorbidities No comorbidity DM HTN Others	 20(55.56%) 8(22.22%) 6(16.67%) 2(5.56%)	 5(35.71%) 3(21.43%) 4(28.57%) 2(14.28%)	 0.432 0.834 0.108 0.091
TSH, mu/L ≤2 >2	 31(86.11%) 5(13.89%)	 14(100%) 0(0%)	0.108
Tg Negative Positive	 16(44.44%) 20(55.56%)	 7(50%) 7(50%)	0.714

DISCUSSION:

According to the results of the present study, PTC accounted for (76%), while the FTC accounted for 24% of patients with malignant thyroid carcinoma. Of note, the other types of thyroid cancers were excluded from the study based on the aims of the study to determine the predictive value of Tg in differentiating between PTC and FTC. This result is in line with global incidence of these malignancies. Because of the parallels in their clinically indolent behavior, care, and outcome, FTC and PTC are frequently examined together in most papers [21]. The reported incidence of FTC varies widely, ranging from 10% to 15% of all differentiated

thyroid carcinomas [22]. Due to differences in dietary iodine concentration, there are significant geographical differences in the relative quantities of FTC. Indeed, in iodine-deficient locations, the prevalence of FTC is significantly higher, accounting for up to 40% of differentiated thyroid cancer cases [21].

Worldwide, different studies demonstrated different diagnostic value of Tg. Preoperative serum Tg has been employed in the differential diagnosis of DTC in previous investigations. Preoperative serum Tg was employed by Petric et al. [23] to differentiate between follicular adenoma and carcinoma, as well as follicular cancer and Hurthle cell carcinoma. The median preoperative Tg concentrations in papillary carcinomas, follicular carcinomas, and Hürthle cell carcinomas were 87, 72, and 106 ng/ml, respectively. In another study, Petric et al. [24] reported that median preoperative Tg concentration in the patients with and without FTC was 407 and 172 ng/ml, respectively. In multivariate analysis, serum Tg concentration was an independent predictive factor of FTC. The patients with preoperative values higher than 400 ng/ml had higher risk of malignancy. In contrast, Suh et al. [25] reported that Tg was not an independent risk factor. In European and American guidelines on the management of patients with differentiated thyroid cancer, serum Tg concentration monitoring is suggested in the follow-up of patients following initial treatment. Preoperative Tg measurement, however, is an insensitive and non-specific diagnostic tool for thyroid cancer, according to the European and American Thyroid Associations[26]. Rasmussen et al. [27] found out a significant correlation between the size of the goiter, presence of multinodularity, intake of iodine and serum

Tg concentration in the subjects with mild-to-moderate iodine deficiency.

Several possible factors might reduce the sensitivity of the TG assay, such as the heterogeneity in the diffusion of Tg, involvement of the heterophile antibody, and the “hook” effect of the detection method, which is an immunogenic phenomenon whereby the effectiveness of Abs in to form immune complex is sometimes impaired when concentrations of an Ab or an Ag are very high. The formation of immune complexes stops increasing with greater concentrations and then decreases with extremely high concentrations, producing a hook shape on a graph of measurements.[28]

Girardi et al. [29] studied 204 benign and 57 malignant thyroid nodules in a retrospective investigation in Brazil. Univariate and multivariate models were used to investigate variables such as age, gender, and ultrasonographic characteristics. Hypoechoic texture (p 0.041) and irregular or lobulated shape (p 0.041) were found to be significant in a univariate model ($p < 0.001$), and ill- defined margins ($p = 0.001$) were significantly associated with cancer. Like in the present study, there was no effect of gender or TSH level. Hulikal et al. [30] also stated that age and gender were not significant variables influencing the differences between benign and malignant groups in their study. Two further investigations [31,32] yielded very identical results.

Petric et al. [24] found that patient age, solitary tumor, and preoperative blood thyroglobulin level were all dependent predictors of thyroid follicular neoplasms. Patient age and preoperative serum Tg levels were independent predictors of malignancy in Hurthle cell neoplasms, according to Strazisar et al. [33]

In the present study, the incidence of post-thyroidectomy complications was found to be 28

The incidence of post-thyroidectomy hypocalcemia varies from 2% to 83% depending on the definition used by the authors. Only symptomatic hypocalcemia is included by some writers, while asymptomatic hypocalcemia associated with temporary hypoparathyroidism is included by others [34,35]. In particular, in an American investigation, the average incidence of definitive hoarseness was determined to be 1.8 percent, with literature reporting rates ranging from 0.7 to 5.65 percent [36].

Limitations

1. The relatively small sample size did not allow the global generalization of the results.
2. Anti-thyroglobulin antibody was not measured which can interfere with the results of thyroglobulin.
3. Other types of differentiated thyroid carcinoma were not included..

CONCLUSION:

1. Thyroglobulin has a moderate sensitivity for detection PTC (60.53%), while it has poor sensitivity for detection FTC (33.33%).
2. The short term post-operative complication of thyroidectomy is 28%, with hypocalcemia was the most common complication.
3. Papillary thyroid carcinoma is more common than FTC among patients undergoing thyroidectomy (76% versus 24%).

Recommendations

1. Thyroglobulin could increase the predictive value of FNAC in preoperative assessment of thyroid cancer especially for PTC.
2. Further studies with larger sample size including other types of thyroid cancer are required for more solid conclusion

REFERENCES:

1. Younis E. Oncogenesis of Thyroid Cancer. Asian Pac J Cancer Prev. 2017; 18:1191-99.
2. Furukawa K, Preston D, Funamoto S, et al. Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. Int J Cancer. 2013;132:1222–26.
3. Nikiforov YE. Radiation-induced thyroid cancer: what we have learned from chernobyl. Endocr Pathol. 2006;17:307–17.
4. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a micro-carcinoma in a patient older than 45 years. Thyroid. 2011; 21:231– 36.
5. Shah JP. Thyroid carcinoma: epidemiology, histology, and diagnosis. Clin Adv Hematol Oncol. 2015;13:3-6.
6. Nishiyama RH, Ludwig GK, Thompson NW. The prevalence of small papillary thyroid carcinomas in 100 consecutive necropsies in an American population. In: DeGroot LJ, editor. Radiation-Associated Thyroid Carcinoma. New York: Grune & Stratton.
7. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. The Lancet.:2016;388:2783-95.
8. Howlader N NA, Krapcho M, Miller D, et al. editors. SEER Cancer Statistics Review, 1975-2013. Bethesda, MD: National Cancer Institute; April 2016. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER website
9. Dralle, Henning et al. "Follicular cell-derived thyroid cancer." *Nature reviews. Disease primers* vol. 1 15077. 10 Dec. 2015, doi:10.1038/nrdp.2015.77.
10. LiVolsi, Virginia A. "Papillary thyroid carcinoma: an update." *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* vol. 24 Suppl 2 (2011): S1-9. doi:10.1038/modpathol.2010.129
11. Lee CC AM, Junit SM, Ng KL, Wong SY, Ramli NSF, Hashim OH. Malignant transformation of benign thyroid nodule is caused by prolonged H2O2 insult that interfered with the STAT3 pathway?. Int J Clin Exp Med. 2016;9:18601-17.
12. McHenry CR, Phitayakorn R. Follicular adenoma and carcinoma of the thyroid gland. Oncologist. 2011;16:585-93.
13. Ahmadi S, Stang M. Hürthle cell carcinoma: Current perspectives. OncoTargets and Therapy. 2016;9:6873 .
14. Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hürthle (oncocytic) cell and its associated pathologic conditions: A surgical pathology and cytopathology review. Archives of Pathology & Laboratory Medicine. 2008;132:1241-50.
15. Goffredo P, Roman SA, Sosa JA. Hurthle cell carcinoma. Cancer.2013;119:504-11.
16. Feldkamp J, Führer D, Luster M, et al. Fine Needle Aspiration in the Investigation of Thyroid Nodules. Dtsch. Arztebl. Int. 2016; 113: 353–59.
17. Schmidbauer B, Menhart K, Hellwig D, Grosse J. Differentiated Thyroid Cancer-Treatment: State of the Art. Int J Mol Sci. 2017;18:1292.
18. Dralle H, Musholt TJ, Schabram J, et al. et al. German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors. Langenbecks Arch. Surg. 2013;398: 347–75.
19. Washington D.C.: American Association for Clinical Chemistry; c2001– 2018. Thyroglobulin; [updated 2017 Nov 9; cited 2018 Aug 8].
20. Asari R, Koperek O, Scheuba C, et al. Follicular thyroid carcinoma in an iodine-replete endemic goiter region: a prospectively collected, retrospectively analyzed clinical trial. Annals of Surgery. 2009;249:1023–31.
21. Lang BH-H, Lo C-Y, Chan W-F, Lam K-Y, Wan K-Y. Prognostic factors in papillary and follicular thyroid carcinoma: their implications for cancer staging. Annals of Surgical Oncol 2007;14:730–38.
22. D"Avanzo A, Treseler P, Ituarte PHG, et al. Follicular thyroid carcinoma: histology and prognosis. Cancer. 2004;100:1123–29.
23. Petric R, Besic H, Besic N. Preoperative serum thyroglobulin concentration as a predictive factor of malignancy in small follicular and Hurthle cell neoplasms of the thyroid gland. World J Surg Oncol 2014;12:282.

24. Petric R, Perhavec A, Gazic B, et al. Preoperative serum thyroglobulin concentration is an independent predictive factor of malignancy in follicular neoplasms of the thyroid gland. J Surg Oncol 2012;105: 351–56.

25. Suh I, Vriens MR, Guerrero MA, et al.: Serum thyroglobulin is a poor diagnostic biomarker of malignancy in follicular and Hurthle-cell neoplasms of the thyroid. Am J Surg 2010;200:41– 46.

26. Cooper DS, Doherty GM, Haugen BR, et al.: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2009;19: 1167–214.

27. Rasmussen LB, Ovesen L, Bu¨low I, et al.: Relations between various measures of iodine intake and thyroid volume, thyroid. nodularity, and serum thyroglobulin. Am J Clin Nutr 2002;76: 1069–76.

28. Ringel, M.D.; Nabhan, F. Approach to follow-up of the patient with differentiated thyroid cancer and positive anti-thyroglobulin antibodies. J. Clin. Endocrinol. Metab. 2013;98:3104–10.

29. Girardi FM, Silva LM, Flores CD. A predictive model to distinguish malignant and benign thyroid nodules based on age, gender and ultrasonographic features. Braz J Otorhinolaryngol. 2019;85:24-31.

30. Hulikal N, Re A, Banoth M, Chowhan AK, Yutla M, Sachan A. Can preoperative serum thyroglobulin levels predict the risk of malignancy? Results from prospective analysis of biochemical predictors of malignancy in thyroid nodules. Acta Otorhinolaryngol Ital. 2020;40:33-37.

31. Park VY, Kim EK, Kwak JY, Yoon JH, Moon HJ Malignancy risk and characteristics of thyroid nodules with two consecutive results of atypia of undetermined significance or follicular lesion of undetermined significance on cytology. Eur Radiol 2015; 25: 2601-7.

32. Teixeira GV, Chikota H, Teixeira T, Manfro G, Pai SI, Tufano RP Incidence of malignancy in thyroid nodules determined to be follicular lesions of undetermined significance on fine-needle aspiration. World J Surg 2012;36:69-74.

33. Strazisar B, Petric R, Sesek M, Zgajnar J, Hocevar M, et al. Predictive factors of carcinoma in 279 patients with Hürthle cell neoplasm of the thyroid gland. J Surg Oncol 2010;101:582-86.

34. Liu J, Sun W, Dong W, et al. Risk factors for post-thyroidectomy haemorrhage: a meta-analysis. Eur J Endocrinol. 2017;176:591–602.

35. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014;101:307–20. 28.

36. Daher R, Lifante JC, Voirin N. et al; CATHY Study Group. Is it possible to limit the risks of thyroid surgery? Ann Endocrinol (Paris). 2015;76:1S16–26.

37. Chiang FY, Wang LF, Huang YF, et al. Recurrent laryngeal nerve palsy after thyroidectomy with routine ident.