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Original Research Article

Combined preoperative serum thyroglobulin level and ACR-thyroid imaging reporting and data system scoring could accurately define malignant thyroid nodules

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ABSTRACT

Background: Evaluation of diagnostic ability of preoperative estimation of serum thyroglobulin (TG) to detect malignant thyroid nodules (TN) in comparison to the American College of Radiology, Thyroid imaging reporting and data system (ACR-TIRADS), fine needle aspiration cytology (FNAC) and intraoperative frozen section (IO-FS).

Methods: 34 patients with ACR-TIRADS 2-4 TN were evaluated preoperatively for identification of malignancy and all underwent total thyroidectomy with bilateral neck block dissection if indicated. Results of preoperative investigations were statistically analyzed using the Receiver operating characteristics (ROC) curve analysis as predictors for malignancy in comparison to postoperative paraffin sections.

Results: Preoperative serum TG levels had 100% sensitivity and negative predictive value, while ACR-TIRADS scoring had 100% specificity and positive predictive value with accuracy rates of 95.35% and 97.67% for TG and TIRADS, respectively. ROC curve analysis defined preoperative ACR-TIRADS class and serum TG as highly diagnostic than FNAC for defining malignancy with non-significant difference between areas under curve for TIRADS and TG. For cases had intermediate risk of malignancy on TIRADS, IO-FS had missed 3, FNAC missed 4, while serum TG levels were very high in the 13 cases and were defined by ROC curve as the only significant predictor for malignancy.

Conclusions: Preoperative estimation of serum TG showed higher diagnostic validity than FNAC, high predictability of cancer and ability to verify the intermediate findings on TIRADS. Combined preoperative TIRADS and TG estimation could accurately discriminate malignant TN with high accuracy and spare the need for preoperative FNAC or IO-FS.

Keywords: Thyroid nodules, Thyroid imaging reporting and data system classification, Thyroglobulin, Fine needle aspiration cytology, Frozen section, Prediction of malignancy

INTRODUCTION

Thyroid nodule has been a common and serious threaten to human health.[1] The prevalence of thyroid nodules is about 1% per life year and about 5 % of the detected nodules are malignant.[2] The progress in diagnostic techniques for thyroid nodules resulted in accumulation of large volumes of examination reports in clinical practice.[1] Thyroid carcinomas are a heterogeneous group of neoplasms which vary in aggressiveness, depending on the histotype, in a wide range from nearly normal life expectancy with papillary carcinoma (PTC) to the few months' survival in case of anaplastic carcinoma.[3] However, more than 50% of patients with PTC have cervical lymph-node metastasis on diagnosis, and up to 30% show nodal recurrence after surgery plus radioactive iodine therapy.[4]

Ultrasonographic classification of thyroid nodules using the American College of Radiology (ACR), Thyroid Imaging Reporting and Data System (TIRADS) depends on the visual and textural characteristics of nodules including composition, shape, size, echogenicity, calcifications, margins, and vascularity.[5] The ACR-TIRADS has higher specificity in comparison to other risk stratification systems, reduces the number of unnecessary biopsies of benign nodules by 19.9-46.5% and the risk of missing significant cancers using ACR-TIRADS can be reduced by the use of the documented recommendations for nodules that do not meet criteria for biopsy.[7]

Thyroglobulin (TG) is a dimeric iodoglycoprotein of 660 kDa, the most abundant thyroid gland protein and is the protein precursor of tetra and tri-iodothyronine (T4, T3), TG processing and secretion is under control of extensive interactions with chaperone, trafficking, and degradation factors that comprises the secretory proteostasis network.[8,9]

Hypothesis

The current study supposes that preoperative estimation of serum thyroglobulin (TG) levels and ACR-TIRADS could spare the invasive procedures for diagnosis of cancer thyroid.

Objectives

Evaluation of the diagnostic ability of preoperative estimation of serum TG to detect malignant thyroid nodules (TN) in comparison to ACR-TIRADS, fine needle aspiration cytology (FNAC) and frozen section.

METHODS

Design

Prospective comparative interventional study.

Setting

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Patients and methods

The current study was conducted according to the conditions of the Local Ethical Committee since June 2017 till September 2020. All patients presenting with TN were vulnerable for evaluation for inclusion and exclusion criteria. After registering the demographic and general clinical data, patients underwent local clinical evaluation and gave blood samples for routine laboratory investigations and estimation of serum TG. Then, patients underwent neck gray scale ultrasonography (US) that was scored according to ACR-TIRADS (10) and FNAC by specialized pathologist.

Patients with thyroid lesions of ACR-TIRADS 2-4 were only included in the study, while patients with ACR-TIRADS ≥5, autoimmune thyroid lesions, skin cutaneous lesions and coagulopathy were excluded from the study. Patients with suspicious US examination (ACR-TIRADS 4a and 4b) underwent intraoperative frozen section (IO-FS).

Surgical technique

All surgical procedures were performed under general inhalational anesthesia with endotracheal intubation. After skin sterilization and patients' positioning, total thyroidectomy was conducted (Figure 1a and 1b) as previously described by Jain and bilateral neck dissection was performed for cases with ACR-TIRADS 4c lesions and lesion that was proved to have cancer thyroid by IO-FS (Figure 2a and 2b).[11] Wound was closed in layers with deep wound drainage using multi-pore vacuum drainage. Patients had received their immediate postoperative (PO) care at the postanesthetic care unit and were transferred to words after assurance of stability of vital signs.

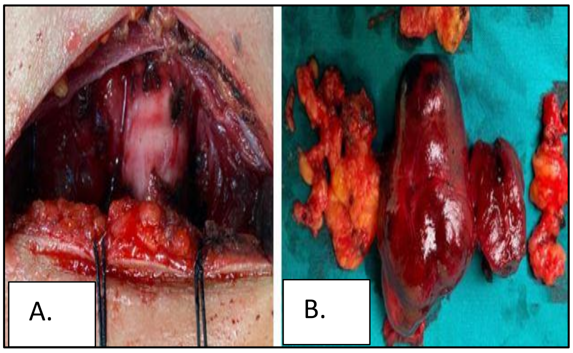

Figure 1: A) Post-thyroidectomy pare trachea. B) Total thyroidectomy with bilateral neck block dissection.

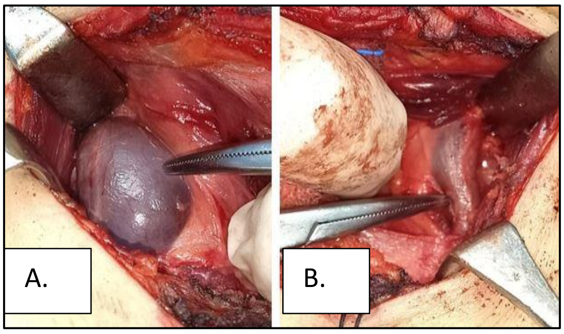

Figure 2: A) Block dissection of left-side lymph nodes. B) Block dissection of Rt-side lymph nodes.

All patients were managed as one-day surgery and were home discharged to re-attend the hospital for drain removal and wound checking. All excised specimens were sent for histopathological examination of paraffin sections (PO-PS) to assure of diagnosis. After complete wound healing, patients who had cancer thyroid were referred to receive their nuclear their radioactive iodine therapy.

Statistical analysis

Obtained data were presented as mean, standard deviation, numbers, percentages, median and interquartile range. Results of preoperative investigations were evaluated as predictors for malignancy using the ROC curve analysis judged by the area under the curve (AUC) compared versus the null hypothesis that AUC=0.05 and paired-analysis of AUC was conducted versus the null hypothesis that AUC=0. Statistical analysis was conducted using the Statistical package for social sciences (SPSS) (Version 26, 2015) for Windows statistical package. P<0.05 was considered statistically significant.

RESULTS

The study included 51 patients with TN; 8 patients were excluded for not fulfilling inclusion criteria and 43 patients were included in the study; patients' demographic data are shown in table 1.

Table 1: Demographic and clinical data of studied patients.

Data		Findings
Age (years)	<40	6 (14%)
	40-50	20 (46.5%)
	>50	17 (39.5%)
	Mean (±SD)	47.8 (5.6)
	Range	31-57
Gender	Male	9 (20.9%)
	Female	34 (79.1%)
Body mass index (kg/m²)	Average (<24.9)	2 (4.7%)
	Overweight (25-30)	21 (48.8%)
	Obese (>30)	20 (46.5%)
	Mean (±SD)	30.2 (3)
	Range	24.3-34.6

According to the ACR-TIRADS classification of TN, 17 TN were scored 0, 4 nodules were scored 1, 9 TN were scored 2 and 13 TN were scored 3. Cytological examination of FNAC aspirate suggested malignancy in samples of 17 nodules (39.5%), and absence of malignant cells in samples of 22 nodules (51.2%) but in the remaining four patients (9.3%) the procedure was cancelled. The median level of preoperative serum TG was 826 ng/ml (IQR: 57.55-821.45). Thirteen patients had IO-FS that detected malignancy in 10 specimens and denied the presence of malignancy in three specimens. PO paraffin sections detected malignancy in 27 specimens and approved the benign pattern in 16 specimens (Table 2).

Evaluation of the diagnostic validity of preoperative investigation in comparison to the results of PO-PS showed that preoperative estimation of serum TG levels had 100% sensitivity and negative predictive value (NPV), while ACR-TIRADS scoring had 100% specificity and positive predictive value (PPV) and both had accuracy of diagnosis of 95.35% and 97.67% for TG and TIRADS, respectively (Table 3).

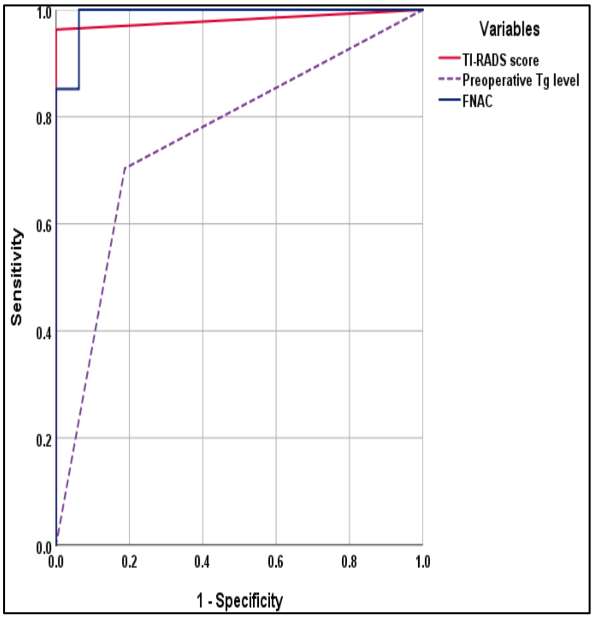

Figure 3: ROC curve analysis of preoperative investigations as predictors for malignancy of TN.

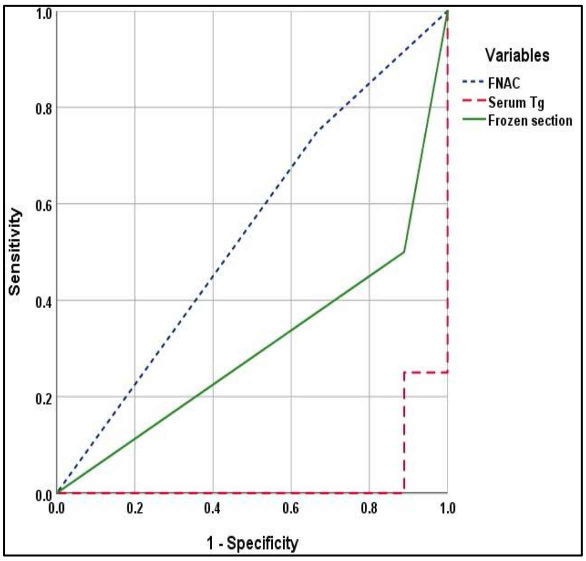

Figure 4: ROC curve analysis for predictors of malignancy in suspicious thyroid nodules on TIRADS.

ROC curve analysis for the three preoperative investigations defined preoperative ACR-TIRADS class and serum TG as highly diagnostic than FNAC for defining malignancy (Figure 1). The paired-sample area difference under the ROC curve showed non-significant between AUC for diagnostic ability of TIRADS classification and estimated serum TG, while the differences were significant between each of TIRADS classification and estimated serum TG and preoperative FNAC (Table 4).

Intraoperative frozen section had missed three cancer cases of the studied 13 cases, which had confirmed to be malignant on PO-PS examination. Comparison of the result of frozen section versus the results of preoperative investigation showed that preoperative TIRADS and serum TG estimation had diagnosed these 13 cases as suspicious with high risk of malignancy, while FNAC missed 4 of these 13 cases. ROC curve analysis for differentiation between preoperative serum TG level, preoperative FNAC and IO-FS for assurance of malignancy among cases suspicious according to TIRADS classification, defined high preoperative serum TG levels as the only significant predictor for malignancy in such cases with AUC= 0.028±0.042 (95% CI: 0.000-0.110, p=0.009), while AUC was 0.306±0.167 (95% CI: 0.000-0.605, p=0.280) for IO-FS and 0.542±0.177 (95% CI: 0.194-0.889, p=0.817) for FNAC (Figure 2).

Table 2: Results of preoperative investigations of studied patients.

TI-RADS classification					
	Score	**Significance**	**Risk of Malignancy**	**Number**	**(%)**
Class 2	0	Noticeably benign pattern	0%	11	25.6
Class 3	0	Probably benign nodules	<5%	6	14
Class 4a	1	Undetermined malignant	5-10%	4	9.3
Class 4b	2	Suspicious for malignancy	10-50%	9	20.9
Class 4c	3	Highly suspicious for malignancy	50-85%	13	30.2
Fine needle aspiration cytology					
Positive for malignancy				17	39.5
Negative for malignancy				22	51.2
Procedure was cancelled				4	9.3
Preoperative serum Thyroglobulin (ng/ml)			Median	IQR	
			628	57.55-821.45	
Intraoperative frozen section			Number	(%)	
Positive for malignancy			10	76.9	
Negative for malignancy			3	23.1	
Postoperative paraffin section			Number	(%)	
Positive for malignancy			27	62.8	
Negative for malignancy			16	37.2	

Table 3: Diagnostic validity characters of the used preoperative investigations in comparison to the results of postoperative paraffin sections as a gold standard for comparison.

	US	FNAC	Serum TG
True positive	26	19	26
False positive	0	3	2
True negative	16	14	15
False negative	1	7	0
Sensitivity	96.3% (95%CI: 81.03-99.91)	73.08% (95%CI: 52.2-88.43%)	100% (95%CI: 86.77-100%)
Specificity	100% (95%CI: 79.41-100)	82.35% (95%CI: 56.57-96.2%)	88.24% (95%CI: 63.56-98.54%)
Positive predictive value	100%	86.36% (95%CI: 68.8-94.78%)	92.86% (95%CI: 77.96-97.95%)
Negative predictive value	94.12% (95%CI: 70.04-99.1)	66.67% (95%CI: 50.57-79.63)	100%
Accuracy	97.67% (95%CI: 87.71-99.94)	76.74% (95%CI: 61.37-88.24)	95.35% (95%CI: 84.19-99.43%)

Table 4: ROC curve analysis for the identification of the best preoperative diagnostic modality for presence of cancer.

ROC curve analysis			
	AUC (SE)	**P value**	**95% CI**
Preoperative serum TG	0.991 (0.011)	<0.001	0.970-1.000
TI-RADS classification	0.981 (0.022)	<0.001	0.939-1.000
FNAC	0.748 (0.077)	0.005	0.606-0.910
Paired-Sample Area Difference under the ROC curves			
	AUC difference (SE)	P value	95% CI
TI-RADS versus FNAC	0.223 (0.293)	0.002	0.083-0.363
Serum TG versus FNAC	0.233 (0.279)	0.001	0.097-0.368
TIRADS versus serum TG	0.009 (0.170)	0.666	0.033-0.051

DISCUSSION

The current study relied for preoperative diagnosis on neck ultrasonographic imaging and differentiation of nodules according to the ACR-TIRADS scores. TIRADS correctly, in relation to the results of PO paraffin section, defined 26 malignant and 16 benign TN and missed only one malignant TN with specificity rate and PPV of 100% and sensitivity rate of 96.3% and NPV 94.12% and ROC curve analysis assured these results. These figures go in hand with Grani et al., who reported that TIRADS allowed the largest reduction of FNAC with a NPV of 97.8% and later on Grani et al., reported that ACR-TIRADS confirmed a significant discriminative performance with a NPV of 100% in patients of all ages and concluded that the use of TIRADS could avoid a sizable number of biopsies when applied as rule-out test.[12,13] Also, Zhang et al., documented that ACR- TIRADS demonstrated higher specificities than the TIRADS proposed by Kwak, and Korean Thyroid Association/Korean Society of Thyroid Radiology (KTA/KSThR) and significantly reduced the number of unnecessary biopsy in all the nodules (10-20 mm) than with the use of the American Thyroid Association and KTA/KSThR guidelines.[14]

Preoperative estimation of serum TG levels, also did better with 100% sensitivity rate and PPV, 88.24% specificity rate and NPV of 92.86%. Moreover, paired-test analysis for AUC for both TIRADS and serum TG level showed non-significant difference a finding indicating similar diagnostic ability of both while in comparison, to AUC for FNAC the difference was significant, thus indicating diagnostic ability superior to that of FNAC. In support of these data, Hasukic et al., detected sensitivity, specificity, PPV and NPV of 66%, 76%, 73% and 69% for FNAC in detection of thyroid malignancy.[15]

Furthermore, in cases with suspicious TIRADS, estimated serum TG level had superior diagnostic ability than that of FNAC and IO-FS. In line with obtained results, DU et al., documented that serum TG level reflects abnormal thyroid function and can indicate the textural abnormalities as the presence of goiter or TN and Patell et al., found preoperative TG correlated significantly with the gland size and the T stage of differentiated thyroid cancer.[16,17]

Recently, Zhong et al., compared the diagnostic validity of serum TG for detection of recurrence of differentiated thyroid cancer versus 131I whole body scan (131I -WBS) and Positron Emission Tomography–Computed Tomography (PET/CT) and found that among 54 TG-positive patients, 49 were positive for 131I-WBS and 32 were positive for PET/CT imaging and all of the 15 TG-negative patients both of 131I-WBS and PET/CT were negative.[18] Also, Hulikal et al., in a series of 100 TN found the median serum TG, TSH and anti-TG levels were 29 ng/ml, 1.6 mIU/L and 1.1 IU/ml, respectively in patients had documented benign lesion, while in those had documented malignant nodules serum levels were 162 ng/ml, 1.7 mIU/L and 0.9 IU/ml, respectively and on ROC curve analysis TG can predict malignancy risk with a 72% sensitivity and 73% specificity, so documented that preoperative TG could be used for predicting risk of malignancy.[19]

The increased serum TG could be attributed to increased rate of nodule growth with subsequent increase of the thyroid gland volume in association with hypothalamic-pituitary system activation and so on.[20]

The obtained results illustrated the importance of the use of combination of preoperative TIRADS and estimated serum TG level to achieve accurate discrimination of cancerous TN. Similarly, Yu et al., (21) using preoperative TG level and US features of TN detected malignant nodules with accuracy, sensitivity and specificity rates of 89.2%, 90.2% and 87.7% and the PPV was 90.7%, which was significantly higher than that of the intraoperative frozen sections and Miao et al., (22) found TG and free thyroid hormones had significant effects on the incidence of malignant nodules in patients and US analysis showed a PPV and NPV of 93.20% and 84.10%, respectively.

Limitations

Estimation of TG-antibody titer was one of the study limitations for being an explanation for low serum TG levels in some patients had malignant TN.

CONCLUSION

The obtained results assured the proposed hypothesis for the use of preoperative estimation of serum TG for its higher diagnostic validity than FNAC, high predictability of cancer and ability to verify the intermediate findings on TIRADS. Thus, using both preoperative TIRADS and TG estimation could accurately discriminate malignant TN with high accuracy and spare the need for preoperative FNAC or intraoperative frozen section.

Recommendations

It is recommended to evaluate the same tools for evaluation of malignancy in thyroid autoimmune disorders. Also, multicenter comparative studies are mandatory to confirm the obtained results.

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REFERENCES

1. Chang L, Fu C, Wu Z, Liu W, Yang S. Data-Driven Analysis of Radiologists' Behavior for Diagnosing Thyroid Nodules. IEEE J Biomed Health Inform. 2020;24(11):3111-123.
2. Kaderli R, Trepp R: [From thyroid nodules to thyroid cancer]. Ther Umsch. 2020;77(9):419-25.
3. Lloyd R, Osamura R, Klöppel G, Rosai J. WHO classification of tumours of endocrine organs, 4th ed., International Agency for Research on Cancer (IARC), Lyon, France.
4. Foppiani L, Sola S, Cabria M, Bottoni G, Piccardo A. Unstimulated Serum Thyroglobulin Levels after Thyroidectomy and Radioiodine Therapy for Intermediate-Risk Thyroid Cancer Are Not Always a Reliable Marker of Lymph Node Recurrence: Case Report and a Lesson for Clinicians. Case Rep Endocrinol. 2020;2020:8827503.
5. Ataide E, Ponugoti N, Illanes A, Schenke S, Kreissl M, Friebe M. Thyroid Nodule Classification for Physician Decision Support Using Machine Learning-Evaluated Geometric and Morphological Features. Sensors (Basel). 2020;20(21):6110.
6. Hoang J, Middleton W, Tessler F: Update on ACR TI-RADS: Successes, Challenges and Future Directions, From the AJR Special Series on Radiology Reporting and Data Systems. AJR Am J Roentgenol. 2020.
7. Kim P, Suh C, Baek J, Chung S, Choi Y, Lee J. Unnecessary thyroid nodule biopsy rates under four ultrasound risk stratification systems: a systematic review and meta-analysis. Eur Radiol. 2020.
8. Citterio C, Morishita Y, Dakka N, Veluswamy B, Arvan P. Relationship between the dimerization of thyroglobulin and its ability to form triiodothyronine. J Biol Chem. 2018;293(13):4860-869.
9. Wright M, Kouba L, Plate L. Thyroglobulin interactome profiling defines altered proteostasis topology associated with thyroid dyshormonogenesis. Mol Cell Proteomics. 2020; mcp.RA120.002168.
10. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab. 2009;94:1748-51.
11. Jain V. Safe and Optimum Steps for Total / Hemi Thyroidectomy. Otolaryngol Open Access J. 2016;1(4):000120.
12. Grani G, Lamartina L, Ascoli V, Bosco D, Biffoni M, Giacomelli L et al. Reducing the Number of Unnecessary Thyroid Biopsies While Improving Diagnostic Accuracy: Toward the "Right" TIRADS. J Clin Endocrinol Metab. 2019;104(1):95-102.
13. Grani G, Brenta G, Trimboli P, Falcone R, Ramundo V, Maranghi M, et al. Sonographic Risk Stratification Systems for Thyroid Nodules as Rule-Out Tests in Older Adults. Cancers (Basel). 2020;12(9):2458.
14. Zhang W, Xu H, Zhang Y, Guo L, Xu S, Zhao C et al. Comparisons of ACR TI-RADS, ATA guidelines, Kwak TI-RADS, and KTA/KSThR guidelines in malignancy risk stratification of thyroid nodules. Clin Hemorheol Microcirc. 2020;75(2):219-32.
15. Hasukic B, Jakubovic-Cickusic A, Sehanovic E, Osmic H. Fine Needle Aspiration Cytology and Thyroglobulin Antibodies in Preoperative Diagnosis of Thyroid Malignancy. Med Arch. 2019;73(6):382-85.
16. DU Y, Gao Y, Feng Z, Meng F, Fan L, Sun D. Serum Thyroglobulin-A Sensitive Biomarker of Iodine Nutrition Status and Affected by Thyroid Abnormalities and Disease in Adult Populations. Biomed Environ Sci. 2017;30(7):508-16.
17. Patell R, Mikhael A, Tabet M, Bena J, Berber E, Nasr C. Assessing the utility of preoperative serum thyroglobulin in differentiated thyroid cancer: a retrospective cohort study. Endocrine. 2018;61(3):506-10.
18. Zhong Y, He J, Zhang C, Ardlee B. Treatment of Differentiated Thyroid Cancer and Recurrent

Laryngeal Nerve Function with 131 Iodine Based on PET / CT Image Segmentation Algorithm. World Neurosurg. 2020;S1878-8750(20)32362-7.
19. Hulikal N, Re A, Banoth M, Chowhan A, 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(1):33-37.
20. Tkachuk N: Thyroid and Pseudothyroid Dysfunction as a Cause that is Promoting the Relapse of Benign Focal Thyroid Pathology. J Med Life. 2020;13(3):426-30.
21. Yu Q, Liu K, Xie C, Ma D, Wu Y, Jiang H, Dai W. Development and validation of a preoperative prediction model for follicular thyroid carcinoma. Clin Endocrinol (Oxf). 2019;91(2):348-55.
22. Miao S, Jing M, Sheng R, Cui D, Lu S, Zhang X et al. The analysis of differential diagnosis of benign and malignant thyroid nodules based on ultrasound reports. Gland Surg. 2020;9(3):653-60.

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