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HEAD, NECK AND DENTAL RADIOLOGY

The impact of TI-RADS in detecting thyroid malignancies: a prospective study

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Abstract

Introduction Thyroid ultrasonography (US) is the first-step noninvasive and easily accessible diagnostic method widely used in the detection and characterization of nodular thyroid disease. We aimed to develop a TI-RADS, which is easy to apply and only relies on the counting of suspicious criteria. In order to measure the reliability of the system, we investigated its correlation with fine needle aspiration biopsy (FNAB) and post-surgery histological results.

Materials and methods In this prospective study, 242 patients who had undergone FNAB with simultaneous cytopathologist in the radiology department between April and August 2016 were analyzed. Before FNAB, the thyroid gland was re-evaluated with US, and TI-RADS classification was made. Demographic characteristics, family thyroid cancer history and radiotherapy history to the neck region were noted.

Results Of the 242 patients, 17.3% were male (42 males/200 females). US-guided FNAB was applied to all patients. Mean age was 50 ± 13 years (min: 19, max: 82). Both FNAB and final post-surgery histology results showed that sex and age were not statistically significantly associated with malignancy ($p = 0.193$) TI-RADS criteria and FNAB results revealed a statistically significant association between irregular contours, the state of anteroposterior diameter being longer than transverse diameter, microcalcifications, marked hypoechogenicity, and malignancy ($p < 0{,}05$). Thirty patients were TI-RADS ≥ 4, 206 patients were TI-RADS ≤ 3 and there was a significant correlation between TI-RADS and Bethesda classification ($p = 0.001$). In addition, statistically significant associations were found between malignancy and family history of thyroid cancer ($p = 0.035$) and radiotherapy history to the neck region ($p = 0.01$).

Conclusion TI-RADS system after nodule identification is based only on the counting of suspicious criteria. It will be safe and effective to recommend follow-up with low score TI-RADS, benign characters and insufficient FNAB results, and thus, unnecessary thyroidectomy operations will be prevented. It will be easier for surgeons to recommend surgery and persuade the patients for it when patients have high TI-RADS scores. TI-RADS has high power in detecting malignancy by recommending biopsy of suspicious nodules.

Keywords Thyroid nodules · TI-RADS · Fine needle aspiration biopsy · Ultrasonography

Introduction

Malignancy is seen in 1 of 20 nodules diagnosed in the thyroid gland [2]. Once the nodule is diagnosed in the thyroid gland, benign nodules should be protected from unnecessary and recurrent biopsies, and treatment should be planned for malignant nodules. Thyroid ultrasonography (US) is the first-step noninvasive and easily accessible diagnostic method widely used in the detection and characterization of nodular thyroid disease [5, 23]. Although FNAB plays an important role in detecting thyroid malignancy, it is a costly and minimally invasive method [9]. Previous studies

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have found that the possibility of the nodule being malignant is directly proportional to the number of suspicious sonographic findings and that malignant nodules demonstrate an average of 2 or 3 suspicious ultrasonography findings [14] Despite the attempt to obtain both sensitive and specific combinations in malignancy prediction with the use of various suspicious US findings, the most accurate and effective guide is still not known and has not established its place in routine clinical practice [1]. Authors have aimed to build a standard reporting and data mining system by making standard ultrasonographic evaluations on thyroid nodules. For this purpose, the thyroid imaging and reporting data system (TI-RADS) was first described by Horvarth et al. who defined 10 different ultrasonographic patterns associated with malignancy for thyroid nodules [13]. Shortly after this study, Park and colleagues proposed a system that classified thyroid nodules according to 12 sonographic features [26]. Afterward, TI-RADS has been redefined with similar attributes to the Breast Imaging and Reporting Data System (BI-RADS) system [22]. US findings associated with malignancy in thyroid nodules are microcalcifications, hypoechogenicity, irregular or microlobulated contour, and the anteroposterior (AP) diameter being bigger than the transverse (TR) diameter (AP/TR > 1). When these findings are considered individually, each is poorly predictive, and only when multiple criteria are evaluated together, the specificity of the US increases [10]. Although there are many reporting systems like BI-RADS which are based on the presence of one or more sonographic criteria associated with malignancy, they are not routinely used in thyroid imaging. The common purpose of all these classifications is to determine whether the nodules require fine needle aspiration biopsy (FNAB) [11].

In this study, we aimed to develop a TI-RADS, which is easy to apply and only relies on the counting of suspicious criteria. In order to measure the reliability of the system, we investigated its correlation with FNAB results. TI-RADS should evaluate the possibility of nodules being benign or malignant, providing a standard way for the clinician to take the next step following the nodule detection.

Materials and methods

Study design and patients

This prospective study was approved by the Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital. Ethics Committee and performed in accordance with the ethical guidelines of the Helsinki Declaration. All patients were given verbal information, and their informed consents were received. The study was prospective and included 242 patients sent to our clinic for FNAB between April and August 2016. FNAB indication was decided by the clinician based on patient's clinical, laboratory and ultrasound findings. FNAB was performed by the same radiologist > 5 years of experience and with the same cytopathologist > 10 years of experience. In order to avoid possible hemorrhagic complications during the FNAB procedure, serum thrombocyte and INR levels of the last 2 weeks were evaluated, and anticoagulant and antiaggregant medications were discontinued for at least 1 week prior to the procedure. Demographic characteristics of the patients such as age and sex, family history of thyroid carcinoma, and radiotherapy history to the neck region were noted on the patient follow-up forms. The occurrence of thyroid cancer in first-degree relatives was considered positive for family history.

Evaluation of the nodules according to TI-RADS

FNAB was planned to be performed to the nodule with the biggest size or the most suspicious features in terms of appearance. Each nodule planned to receive FNAB was re-evaluated with US and categorized according to the TI-RADS classification.

Microcalcifications, marked hypoechogenicity, irregular or microlobulated contour, and the anteroposterior (AP) diameter being bigger than the transverse (TR) diameter (AP/TR > 1) were accepted as the malignancy criteria for TI-RADS (Table 1). Echogenicity was classified as hyperechoic, isoechoic, hypoechoic, heterogeneous echoic, and marked hypoechoic. If the echogenicity of the nodule was more hypoechoic than the adjacent strap muscle, the nodule was recorded as marked hypoechoic. The contour structure of the nodule was categorized as well margined, microlobulated contour, and irregularly margined. Calcification foci in the nodule were defined as microcalcification and macrocalcification. Calcifications smaller than 1 mm in size were defined as microcalcifications while those bigger than 1 mm were defined as macrocalcifications. If the nodule had both micro- and macrocalcifications, it was considered as containing microcalcification. Dimensions of the nodule were defined as long AP diameter, long TR diameter, and round shaped.

The parenchyma of a normal thyroid gland was evaluated as TI-RADS 1. Benign lesions of the thyroid gland including simple anechoic cysts, colloid cysts, and isoechoic

Table 1 TI-RADS suspicious criteria

Markedhy poechogenicity
AP diameter > TR diameter
Microlobulated contour/Irregularly marginated
Microcalcification

AP anteroposterior, *TR* transverse

spongiform nodules were classified as TI-RADS 2. Those without suspicious TI-RADS criteria as isoechoic, hypoechoic, hyperechoic encapsulated solid nodules or solid nodules containing cystic component were defined as TI-RADS 3. Nodules with one of the suspicious TI-RADS criteria were TI-RADS 4a, nodules with two of the criteria were TI-RADS 4b, those with three were TI-RADS 4c, and those with four were regarded as TI-RADS 5. Nodules with previously proven malignancy via biopsy were accepted as TI-RADS 6.

FNAB technique

FNAB was performed under the guidance of a Toshiba APLIO 500 ultrasonic device and a linear probe (10 L, 3.5–9.5 MHz). The patients were placed in supine position with their heads in hyperextension, antiseptic cleaning was performed with 10% povidone–iodine solution, and the probe covered with a sterile sheath. For aspiration, dental needle (27G) with 2 mL plastic disposable syringe attached to its rear was used. Entry was performed into the nodule accompanied by the ultrasonography device. Each nodule was aspirated at least twice while inside the nodule.

Evaluation of FNAB materials

Smears were stained, and sufficiency was evaluated bedside by the cytopathologist. In cases where the cytopathologist declared insufficiency and patient compliance permitted, some nodules were entered for the third and fourth time. Due to patient compliance and time constraints, no patient was subjected to more than four entries. FNAB materials were reported according to the BETHESDA system.

Second FNAB sessions was applied to 31 patients who had a non-diagnostic cytology report, or a report of atypia of undetermined significance/follicular lesion of undetermined significance. Pathological diagnosis was obtained in the second biopsy in 29 patients. Six patients who received a non-diagnostic cytology report at the second biopsy were included in the study because they had undergone thyroidectomy and had a pathological diagnosis. Five non-operated patients with non-diagnostic cytology reports for the second time were excluded from the study. Materials of the thyroid surgery patients were examined and diagnosed according to World Health Organization's histological classification of thyroid tumors in 2004.

Statistical analysis

In the statistical analysis of the results; mean, standard deviation, median, maximum and minimum values were used as descriptive statistics for numeric data, and numbers and percentage values were used for categorical data. Correlations between numerical data were evaluated via Spearman's correlation coefficient assuming normal distribution criterion. Statistical difference between the categorical data was tested by Fisher's exact chi-square test. All analyses were performed at 95% confidence level. $p < 0.05$ was considered statistically significant. Statistical data editing and analyses were performed with SPSS 20.0 (IBM Company, USA) software.

Results

Patient demographics

Two hundred and forty-two patients were included into the study, consisting of 17.3% male and 82.7% female (42/200) patients. US-guided FNAB was applied to a total of 242 nodules. Mean age of the patients was 50 ± 13 years (min: 19, max: 82). Both FNAB and final post-surgery histology results showed that sex and age were not statistically significantly associated with malignancy ($p = 0.193$).

TI-RADS and histological evaluation

Evaluation of the association between TI-RADS criteria and FNAB results revealed a statistically significant association between irregular contours, the state of anteroposterior diameter being longer than transverse diameter, microcalcifications, marked hypoechogenicity, and malignancy ($p < 0.05$) (Table 2). FNAB results of the nodules according to Bethesda by TI-RADS categories are given in Table 3 (Benign: 71%, AUS-FLUS:21%). Final pathology results are given in Table 4.

Isoechoic spongiform nodule with benign FNAB result, categorized TI-RADS 2 is seen in Fig. 1. The FNAB result of the isoechoic solid nodule without suspicious criteria as seen in Fig. 2 and hypoechoic solid nodule with cystic components as seen in Fig. 3 which were evaluated as TI-RADS 3 was reported as benign. Hypoechoic solid nodule with microcalcification categorized TI-RADS 4a as seen in Fig. 4 and FNAB result was malign. The isoechoic solid nodule seen in Fig. 5 which has microlobulated contour and microcalcification defined as TI-RADS 4b with suspicious for follicular neoplasm of FNAB result. A nodule with discordance between TI-RADS and FNAB results is also seen in Fig. 6. We defined as TI-RADS- 4b due to the suspicious criteria of the solid nodule like marked hypoechoic, irregular margined, the FNAB result was benign (Fig. 6).

In thyroid cytopathology, an "indetermined group" was created, which was considered "gray zone" and could not be included in the benign or malignant group. These subgroups were "undetermined atypia" or "undetermined follicular lesion"; "follicular neoplasia" or "suspicion of follicular

Table 2 TI-RADS suspicious criteria and FNAB results correlations

	Malign	Benign	Total	*p* value
Margin				
Well marginated	0	216	216	($p < 0.05$)
Irregular margin	7	11	18	
Microlobulated margin	1	7	8	
Total	8	234	242	
Shape				
TR diameter is bigger	5	227	232	($p < 0.05$)
AP diameter is bigger	3	3	6	
Rounded	0	4	4	
Total	8	234	242	
Calcification				
None	2	145	147	($p < 0.05$)
Micro	5	34	39	
Macro	1	55	56	
Total	8	234	242	
Echo				
Hypoechoic	2	121	123	($p < 0.05$)
Hyperechoic	0	20	20	
isoechoic	0	83	83	
Marked hypoechoic	6	1	7	
Heterogenous	0	9	9	
Total	8	234	242	

Table 4 TI-RADS and pathology results after surgery

	Malign	Benign
TI-RADS 2	0	5
TI-RADS 3	0	15
TI-RADS 4a	6	0
TI-RADS 4b	1	0
TI-RADS 4c	6	0
TI-RADS 5	1	0
Total	14 (41.1%)	20 (58.9%)

Fig. 1 Isoechoic spongiform nodule as TI-RADS 2

neoplasia" and "suspicion of malignancy." Six nodules reported as non-diagnostic cytology were excluded from the nodules in total. FNAB results of 236 nodules were classified as benign, malignant and indetermined. TI-RADS distribution of "benign," "malignant" and "indetermined" groups is given in Table 5. There were 30 patients of TI-RADS ≥ 4 and 206 patients of TI-RADS ≤ 3, and there was a significant correlation between TI-RADS and Bethesda classification ($p = 0.001$). According to Bethesda, when the group of 55 indeterminate patients were excluded from the evaluated 236 nodules, FNAB results of the malignant or benign nodules correlated with TI-RADS scores, which can solely be used as a criterion to detect malignancy (Pearson correlation: 0.473). In terms of the correlation of each parameter analyzed with the final FNAB results, statistically significant associations were found in the analyses between malignancy and the presence of thyroid cancer in the patient's family history($p = 0.035$) and prior application of radiotherapy to the neck region ($p = 0.01$). However, in multivariate analyses, both family history and radiotherapy to the neck history were insufficient alone in detecting malignancy as independent variables.

Of the 34 operated patients, 14 (41.1%) were malignant (9 papillary carcinoma, 3 follicular carcinoma, 1 medullary carcinoma, 1 papillary carcinoma follicular variant) and 20 (58.9%) patients were reported as benign (nodular hyperplasia) post-surgery histology results. When the TI-RADS classification of the 20 patients with benign pathology results

Table 3 FNAB results by TI-RADS categories according to Bethesda, AUS: Atypia of undetermined significance, FLUS: Follicular lesion of undetermined significance

	Benign	AUS/FLUS	Suspicious for follicular neoplasm	Suspicious for malignancy	Malign	Non-diagnostic
TI-RADS 2	54	4	0	0	0	2
TI-RADS 3	96	29	0	0	0	3
TI-RADS 4a	21	12	3	1	2	0
TI-RADS 4b	2	5	1	0	0	0
TI-RADS 4c	0	0	0	0	5	1
TI-RADS 5	0	0	0	0	1	0
Total	173 (71%)	50 (21%)	4 (2%)	1 (0.4%)	8 (4%)	6 (1.6%)

Fig. 2 Isoechoic solid nodule as TI-RADS 3

Fig. 3 Hypoechoic solid nodule with cystic components as TI-RADS 3

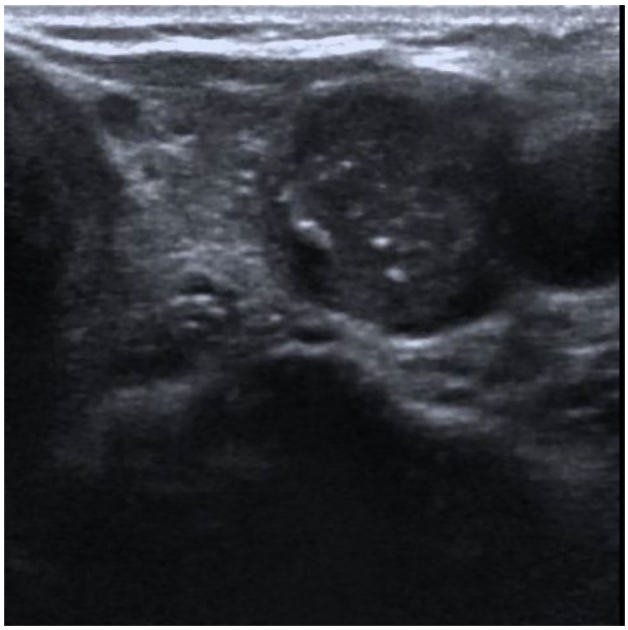

Fig. 4 Hypoechoic solid nodule with microcalcification as TI-RADS 4a

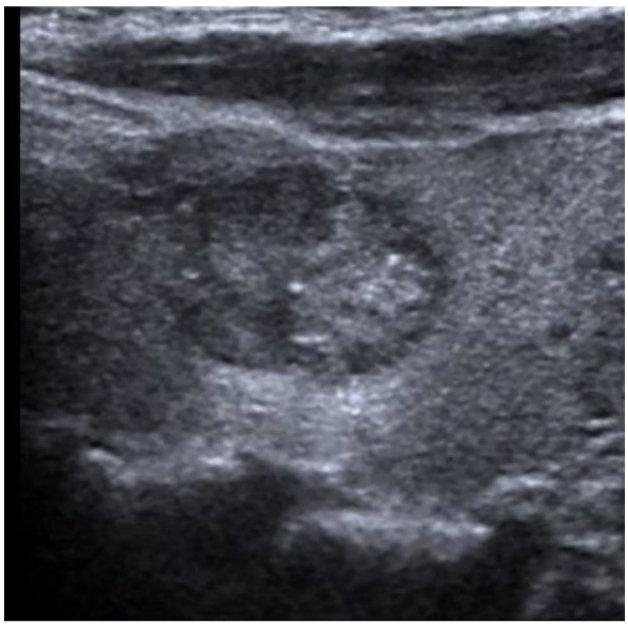

Fig. 5 Isoechoic solid nodule with microlobulated contour and microcalcification as TI-RADS 4b

was checked, all patients were found to be in TI-RADS 2 and 3 categories.

Sensitivity and specificity values of each suspicious criteria of TI-RADS for thyroid cancer evaluated. The sensitivity of "microcalcification," "irregular margin or microlobulated margin," "marked hypoechogenicity," "AP diameter > TR Diameter" were, respectively, 63%, 100%, 7.5%, 37.5%. The specificity of "microcalcification," "irregular margin or microlobulated margin," "marked hypoechogenicity," "AP diameter > TR Diameter" were, respectively, 85%, 92%, 99.5%, 98.7% (Table 6).

There were no malignancies in TI-RADS 1, 2 and 3 categories. Malignancy rates in TI-RADS 4a, TI-RADS 4b, TI-RADS 4c, TI-RADS 5 were 5.1%, 0%, 83.3%, 100%, respectively (Table 7).

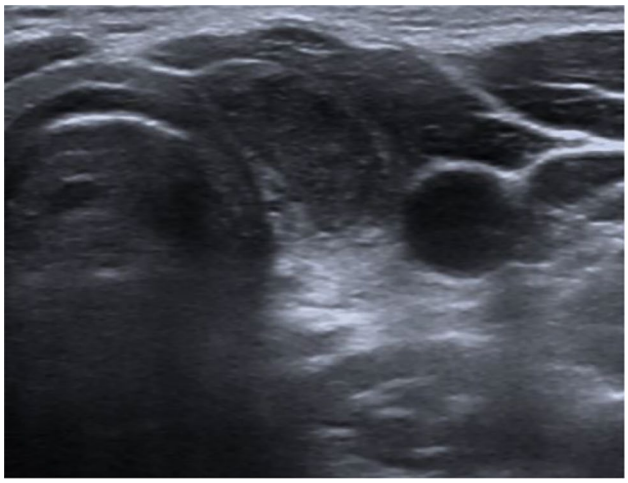

Fig. 6 Marked hypoechoic, irregular margined solid nodule with TI-RADS 4b. The FNAB result was benign cytology

Table 5 TI-RADS categories and benign, malign and indetermined distribution according to Bethesda

	TI-RADS ≤ 3 (TI-RADS 1, 2, 3)	TI-RADS ≥ 4 (TI-RADS 4, 5, 6)	*p* value
Benign	173	0	< 0.05
Indetermined	33	22	0.62
Malign	0	8	< 0.05
Total	206	30	$p = 0.001$

Discussion

In this study and in previously defined systems, TI-RADS1 is defined as normal thyroid gland. TI-RADS2 describes benign lesions of the thyroid gland and does not require biopsy. TI-RADS3 describes the possibly benign lesions of the thyroid gland. There is no need to perform biopsy in this group, as well. TI-RADS4 defines the lesions of the thyroid gland that are suspected of being malignant and have subgroups of 4a, 4b, and 4c. TI-RADS5 defines the possibly malignant lesions of the thyroid gland. For TI-RADS4 and TI-RADS5 categories, it is absolutely necessary to apply FNAB [13]. TI-RADS6 defines the lesions of the thyroid gland that have malignancy proven by biopsy. Recently, American College of Radiology declined TI-RADS categorized as benign, minimally suspicious for malignancy, moderately suspicious for malignancy or highly suspicious for malignancy. ACR TI-RADS is based on criteria like calcifications, margin, shape, echogenicity, and solidity. All sonographic features have additional points, and the total point determines the ACR TI-RADS level of the nodule [8]. Moreover, EU-TIRADS by the European Thyroid Association and K-TIRADS by the Korean Society of Thyroid Radiology are defined. All of these classifications are very successful in demonstrating thyroid malignancy [18].

In our study, a statistically significant relationship was found between malignancy and the presence of microcalcifications, the anteroposterior diameter being longer than the transverse diameter, irregular borders or microlobulated contours and marked hypoechogenicity; however, when the sensitivity and specificity of each of the suspicious TI-RADS criteria were taken into consideration, both in our study and those in the literature, all of these criteria turned out to have low rates of sensitivity in different proportions. Therefore, instead of being used as criteria of malignancy by themselves, we believe it would be wiser if they were grouped together for use along with a reporting system indicating the probability of malignancy for each nodule. The specificity and sensitivity values of suspicious criteria indicated in Table 6 are those conducted by Frates et al. and in this study. In our study, no malignant nodules were seen in the TI-RADS2 group, and the malignancy rate was found to be 0% as in the studies of Horvarth et al. and Kwak et al. (Table 7). In this study, malignancy rate was found to be 0%, which is lower than the literature in the TI-RADS3 category. This is actually a very good result for the TI-RADS3 group, for which we recommend follow-up instead of biopsy. However, since the number of patients in other studies is

Table 6 Sensitivity and specificity values of suspicious criteria for thyroid cancer

	Sensitivity* (%)	Specificity* (%)	Sensitivity Güldoğan et al. (%)	Specificity Güldoğan et al. (%)
Microcalcification	26.1–59.1	85.8–95	63	85
Irregular margin or microlobulated margin	17.4–77.5	38.9–85	100	92
Marked hypoechogenicity	26.5–87.1	43.4–94.3	7.5	99.5
APdiameter > TR diameter	32.7	92.5	37.5	98.7

AP anteroposterior, *TR* transverse

*Frates MC, Benson CB, Charboneau JW, et al. Management of the thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005; 237 (3):794–800

Table 7 Malignancy ratios according to FNAB

	Horvarth et al. (%)	Kwak et al. (%)	Güldoğan et al. (%)
TI-RADS 1	0	0	0
TI-RADS 2	0	0	0
TI-RADS 3	5	1.7	0
TI-RADS 4a	5–10	3.6–12.7	5.1
TI-RADS 4b	10–80	6.8–37.8	0
TI-RADS 4c	10–80	44–72	83.3
TI-RADS 5	80	88.7–97.9	100

much higher compared to this study, we are of the opinion that malign nodules could have been seen in the TI-RADS3 groups and we could have achieved similar results if we had had a higher number of patients. Malignancy rates in the TI-RADS4a group are also similar to other studies (Table 7). In this study, according to the results of the FNAB, malignancy rate in TI-RADS4b was found to be 0%, but when the patients of this group were evaluated, only 2 of the 6 patients turned out with benign FNAB results, along with one suspected follicular neoplasia and three AUS/FLUS (atypia of undetermined significance/ follicular lesion of undetermined significance) diagnoses via FNAB results. One patient in this group had thyroidectomy operation and was reported as malignant in post-surgery histology diagnosis, and malignancy rate was 16.6% according to post-surgery histology results in the TI-RADS4b group. With post-surgery pathology results, our malignancy rates in TI-RADS4b were found to be close to the previous studies. TI-RADS4c malignancy rates were similar to other studies. TI-RADS5 malignancy rate was 100%. In another prospective study by Zhang et al., similar to this one, malignancy rates in nodules smaller than 10 mm have been found to be 100% in TI-RADS5. Although malignancy rates of each group in the TI-RADS categories differed, there was a statistically strong and significant relationship between malignancy and TI-RADS in all of the studies and also in this one. While high TI-RADS scores correlated with malignancy, low TI-RADS scores were found to correlate with benign nature [7, 13, 15, 22, 27, 28].

It is not recommended, due to cost and time, to perform FNAB for every nodule. According to the TI-RADS system, there is no need to apply FNAB to TI-RADS2 category [13]. There is no need for FNAB in the TI-RADS3 category either, but follow-up is recommended, and it is safe to put aside biopsy and prefer follow-up instead. When TI-RADS distribution of all of the patient population included in the study was examined, 188 patients out of 242 (77.6%) were in TI-RADS2 and 3 groups and 54 (22.4%) were in the TI-RADS4 and 5 groups. If the 242 patients included in the study had been evaluated using TI-RADS classification, only 54 patients with nodules classified as TI-RADS4 or 5 would have had a biopsy. Accordingly, the number of biopsies would have decreased by 77.6%. In addition, in this study, there were 173 benign nodules according to FNAB results. If TI-RADS system had been used, follow-up should have been recommended to 150 nodules classified as TI-RADS 2 or TI-RADS 3 out of the 173 benign nodules that underwent FNAB (some of them twice), and FNAB should have been performed to only 23 nodules in TI-RADS4a and 4b groups. With the introduction of the TI-RADS system into clinical practice, biopsies applied to benign nodules will decrease by 86.8% based on the findings of this study.

In the surgical literature, thyroid surgery is recommended to patients who have AUS/FLUS and/or non-diagnostic cytology, which means no result despite having FNAB twice [12]. Of the 34 operated patients presented in this study, 14 (41.1%) were malignant and 20 (58.9%) patients were reported as benign thanks to post-surgery histology results. When the TI-RADS classification of the 20 patients with benign pathology results was checked, all patients were found to be in the TI-RADS2 and 3 categories. That is, 20 patients who should have been followed up according to TI-RADS underwent thyroid surgery because of no clear result with FNAB. This is not an effective approach because of the high costs of surgery and consequences to the patient such as anxiety and loss of work power. In addition, there are post-thyroidectomy complications such as hypocalcemia and recurrent nerve injury, and the patient is obliged to life-long thyroid medications [6]. However, if the TI-RADS system were used in clinical practice, these 20 operated patients would be followed up safely only with US. Thus, thyroidectomy operations that were not really necessary would be prevented. If that were the case, the operation rate would have decreased to 5.7% from 14% in all of the patient population included in this study.

Six patients participating in this study, whose FNAB pathology reports came twice as non-diagnostic cytology, underwent thyroidectomy operation. Five operated patients whose final pathology results were benign had nodules in the TI-RADS 2 and 3 categories. The final pathology result of 1 patient in the TI-RADS 4c category was reported as malignant. It is not always easy to decide on the next step in patients with non-diagnostic cytology reports and to convince a patient for surgery. Recommending follow-up instead of thyroid surgery to the nodules with TI-RADS scores of 2 and 3 was found to be safe according to the results of this study and would be a much more appropriate approach in terms of time and cost. Given the rates of malignancy in Bethesda, the risk to be taken when using TI-RADS is not very high. Previous studies have suggested that malignancy risk is present even in nodules reported as benign according to Bethesda [21].

US for TI-RADS classification and FNAB were performed by the same person and suspicious TI-RADS criteria

were evaluated with the same point of view in our study. The frequently mentioned concerns of operator-dependent and interpersonal differences of interpretation in US examinations were eliminated in this way. Similarly, the materials were evaluated by a single cytopathologist with the same standards, and all were reported in accordance with the Bethesda system. It has been observed that non-diagnostic results reduce with on-site assessment of the pathologist while FNAB is applied [20]. Furthermore, in the study by Yoon et al. it has been observed that the number of non-diagnostic cytology outcomes is much lower when Bethesda is used [27]. Likewise, our rate of non-diagnostic cytology was also quite low (2.5%) when compared to the literature [3, 8].

The relationship between malignancy and the patient having a family history of thyroid cancer was found to be statistically significant when compared both with FNAB results and with post-surgery histology results. Additionally, family history was found to have a low sensitivity of 12.5% and a high specificity of 98% in detecting malignancy. According to FNAB results, the relationship between malignancy and previous radiotherapy to the neck region was found to be statistically significant, but when compared with post-surgery histological results, the relationship with malignancy was not statistically significant. Additionally, in multivariate analyses, both family history and application of radiotherapy to the neck were insufficient alone in detecting malignancy as independent variables. In TI-RADS classification; although it differs in various studies, malignancy is detected in TI-RADS 3 category up to %5. If clinical findings evoke suspicion in TI-RADS 3 category, FNAB may be applied to certain patients to find malignant nodules. In the cases with family history of thyroid cancer and prior application of radiotherapy to the neck region, we suggest it would be appropriate to apply biopsy even if the nodule is in TI-RADS 3 category. Through this approach, diagnosis can be made to the low number of malignant nodules in the TI-RADS 3 category.

There are recent publications showing that contrast-enhanced ultrasound (CEUS) and sonoelastography (USE) have high predictive values in detecting thyroid malignancy, especially when used together [17]. Kwak and colleagues suggest that in addition to the criteria in this study, if possible, solidity measured by USE should also be among the suspicious criteria in the TI-RADS [15]. In a USE examination, benign nodules are 1.7 times harder than the surrounding thyroid tissue and malignant ones are 5 times harder [16]. The most important criterion for USE is that the border of the nodule to be studied must be clearly distinguished from the other nodules around it. In cases of thyroiditis that can cause hardness in the surrounding tissue, or in multinodular cases with a tendency to merge and has no surrounding tissue, incorrect results may be observed [23]. In addition, USE cut-off values for thyroid nodules have not been determined yet, but they vary according to the USE practitioner, experience and device status [4]. Applying USE and CEUS on every nodule in the thyroid gland would have increased the workload and diminish the applicability of TI-RADS, and as most patients had thyroiditis, we didn't include solidity measured with elastography and CEUS among the suspicious criteria in this study. Already according to 2018 EFSUMB non-hepatic elastography guideline, the relevance in the malignant / benign differential diagnosis remains unclear [25].

It is known that malignant lesions of the thyroid are very slow-growing tumors. For this reason, in patients without thyroidectomy, it takes a long period of follow-up to declare a nodule as benign [24]. Thus, Horvath et al. proposed to accept US findings and FNAB results that remain unchanged after 4–5 years of follow-up as an indicator of a benign nodule [1]. In this study, the patients were not followed up for a long time and the strength of TI-RADS classification was evaluated according to FNAB results. This is one of the limitations of our study. However, post-surgery histology results of a limited number of operated patients were also statistically analyzed for each parameter in our study.

Kwak et al. have defined TI-RADS classification and evaluated its correlation with malignancy with 3674 nodules, which means a very distinct superiority in numbers in comparison with this study conducted with 242 patients. This is another limitation of our study; however, it was conducted prospectively while the study of Kwak et al. had a retrospective design [18, 19].

Conclusion

TI-RADS is an easy-to-apply, guiding and safe system after nodule identification based only on the counting of suspicious criteria. Using TI-RADS will create a common terminology in US reports. Moreover, it will be easier for surgeons to recommend surgery and persuade the patients for it when the patients have high TI-RADS scores. Thus, in the cases where FNAB results fail to provide a diagnosis, concerns about missing possible malignancy will be eliminated.

We need more studies on TI-RADS and the eventual utilization of it and when a nodule is diagnosed in the thyroid gland, it will become much easier to decide between biopsy or follow-up (Table 8). TI-RADS works without creating extra workload during thyroid US application, decreases workload and cost by recommending follow-up to benign nodules instead of biopsy for each nodule, and has high power in detecting malignancy by recommending biopsy of suspicious nodules.

Table 8 Thyroid nodule algorithm according to TI-RADS

Category of TI-RADS	Next step
TI-RADS 1	No need for follow-up
TI-RADS 2	No need for follow-up
TI-RADS 3	Follow-up but ⇒ biopsy if family history or radiotherapy history to the neck is positive
TI-RADS 4	Biopsy
TI-RADS 5	Biopsy
TI-RADS 6	Biopsy

Appendices

1. Marked hypoechogenicity, AP diameter > TR diameter, microlobulated contour/ irregularly marginated, microcalcification are defined as suspicious criteria of TI-RADS and it is safe to follow-up the nodules without these criteria.
2. TI-RADS in this study will provide unnecessary biopsies and operations to benign nodules.
3. TI-RADS and the eventual utilization of it, when a nodule is diagnosed in the thyroid gland, it will become much easier to decide between biopsy or follow-up.

Authors' contributions Esra Soyer Güldoğan and Baki Hekimoğlu contributed to concept and wrote the manuscript. Esra Soyer Güldoğan and Onur Ergun contributed to design. Baki Hekimoğlu and Onur Ergun helped in supervision. Esra Soyer Güldoğan, Onur Ergun, Hasan Ali Durmaz, and Kerim Bora Yılmaz contributed to resource. Esra Soyer Güldoğan and Tuğba Taşkın Türkmenoğlu collected and/or processed the data. Esra Soyer Güldoğan and Tuba Akdağ contributed to analysis and/or ınterpretation. Esra Soyer Güldoğan, Tuba Akdağ, and Serra Özbal Güneş contributed to literature search. Baki Hekimoğlu contributed to critical reviews.

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Declarations

Competing interest The authors declare no conflict of interest/competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (including name of committee + reference number) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board.

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