THE ROLE OF SUPERB MICROVASCULAR IMAGING AND SHEAR WAVE ELASTOGRAPHY IN DIFFERENTIATION OF THYROID NODULES FROM INTRATHYROIDAL ECTOPIC THYMUS IN CHILDREN

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Abstract

Background. Ectopic thymus could be located intrathyroidal, therefore fine ultrasound details are useful for this differentiation.

Aim. To investigate differences in stiffness and vascularity properties among thyroid nodules and intrathyroidal ectopic thymus (IET) by obtaining quantitative data in children.

Patients and Methods. Twenty-seven thyroid nodules and 20 IET in children were evaluated in terms of vascularity index (VI) via superb microvascular imaging (SMI) and stiffness by shear wave elastography (SWE). Differences in the volume, VI, and SWE parameters of the lesions were assessed by using the Mann-Whitney U test. Association of the age, lesion volume, SWE, and VI parameters was investigated by using Spearman's correlation analysis. The optimal cut-off values for stiffness and vascularity in the differentiation of nodules from IET were calculated with ROC analysis.

Results. The median (range) age of the participants with thyroid nodules and IET were 15.6 (10-18) years and 8.8 (3-14) years, respectively. The medians (range) VI of the IET and thyroid nodules were 4.7 (0.2-16) % and 23.8 (7.5-40)%, respectively. The median SWE values were 7.6 (4.4-9.5) kPa and 15.58 (8.5-23.4) kPa for IET and nodules, respectively. There have been highly significant differences among medians of volume, SWE, and VI values of the lesions. Significant positive correlations were found between VI and SWE parameters ($p=0.001$, $r=0.64$), and volume with VI ($p=0.018$, $r=0.34$) and SWE ($p=0.001$, $r=0.5$). The diagnostic accuracies were 93%, 91% with the cut-off values as 9.2 kPa, 13% for the SWE and SMI, respectively. IETs were found to be less vascular and less stiff than thyroid nodules.

Conclusions. IETs could be easily and confidently differentiated from nodules using SWE and SMI quantifications. This discrimination prompts the reduction of unnecessary interventional procedures.

Keywords: intrathyroidal ectopic thymus, thyroid nodule, superb microvascular imaging, shear wave elastography, children.

INTRODUCTION

The thymus is a primary lymphoid organ originating from the third and fourth pharyngeal pouches. It separates from the pharynx in the later stages of development and combines with its contralateral part in the superior mediastinum (1). The accessory thymus is an anomaly characterized by the detachment of a part of the thymus during migration. They may be in the form of mediastinal lobes or as islets of tissue from the angle of the mandible to the diaphragm as classical cervico-mediastinal lobules, extracapsular mediastinal lobes, lateral to the phrenic nerve, islands in mediastinal adipose tissue, within cervical fat tissue, in the aortopulmonary window, as accessory cervical lobe, at retrothyroid region and posterior to the innominate vein in descending order (2).

The thyroid gland develops at the base of the primitive pharynx between the first and second pouches on the 24th day of gestation, during the development of the branchial arch and pharyngeal pouches (3). A diverticulum from the root of the tongue develops and the distal lumen of the diverticulum closes with the rapid proliferation of cells growing both ventrally and laterally, constituting the thyroid gland. Undescended thymus and less commonly undescended thyroid tissue, which can be distinguished from each other ultrasonographically owing to their internal echogenicity features, often exist anterolaterally in the neck (Fig. 1a). Although thyroid and thymus glands originate from different pharyngeal pouches, ectopic thymus tissue can be found within the thyroid gland or as a surrounding tissue around the thyroid due to the migration process of the thymus. Intrathyroidal ectopic thymus (IET) tissue is commonly observed as abutting the posterior borders of the thyroid gland lower pole or around the lower pole as a round, oval, triangular, longitudinal, or irregular shaped hypoechoic tissue with tiny punctate echogenicities on

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ultrasound. Additionally, the IET does not present a mass effect and would display fewer vascular structures compared to the thyroid gland without any displacement (Fig. 1b). Thyroid nodule in the differential diagnosis of IET is of oval or spherical morphology, while the geographic, longitudinal, or irregular shape is not expected. On the Doppler ultrasonography evaluation, the displaced vessels, rim vascularity along increased intralesional vascularity are the ultrasonographic findings indicated by the thyroid nodules (Fig. 1c). The lesion, located in the middle part or inferior pole of the thyroid gland, usually in the middle or posterior aspect, having a sharply demarcated geographical, triangular, or longitudinal shape, hypoechogenic and less vascular compared to the thyroid gland, with tiny internal echoes, suggests intrathyroidal thymic inclusion.

IET has previously been reported as a very common incidental finding in children as 2.6% in a survey of thyroid glands of 350 infants and necropsies (4). The incidence of IET has been found to be 0.91% to 17.3% in other recent studies (5-7). The imaging properties of IETs detected on grayscale ultrasonography are widely known among pediatric radiologists. However, IETs detected in centers with limited experience in this field can be misdiagnosed as thyroid nodules and these lesions can be referred for fine-needle aspiration biopsy even if they do not require follow-up. There have been descriptive imaging findings addressing IET diagnosis qualitatively (5-8). However, insufficient data are showing that it is possible to distinguish IET and thyroid nodules in children, quantitatively. A recent study evaluated IET by strain elastography regarding the elasticity properties of IET compared to the surrounding thyroid parenchyma (9). Viscoelastic tissue properties such as tissue stiffness and vascularity would help to depict the tissue characteristics or origin of the lesions. As far as we know, there is no available data in the literature regarding the comparison of vascularity and shear wave elastography (SWE) properties of IETs with thyroid nodules. In this study, we aimed to reveal the quantitative differences in vascularity and elasticity properties of thyroid nodules compared to IETs in children with superb microvascular imaging (SMI) and SWE.

MATERIAL AND METHODS

Patient Selection and Research Protocol

Consecutive 27 children (17 female, 10 male; median age: 15.6 years (range: 10-18) with thyroid nodules and 20 children with IETs (14 male, 6 female; median age: 8.8 years (range:3-14) were evaluated

between August 2017 and August 2018 in the Pediatric Radiology Department. The local ethics committee approved the study (Approval number: 2018/703) and informed consent from the legal guardians of the patients was obtained. Inclusion criteria for the thyroid nodules were a presenting pure solid internal structure without cystic or necrotic changes. IETs were diagnosed by a pediatric radiologist having more than 7 years of radiology and 3 years of pediatric radiology experience owing to descriptive parameters identified for IET as the location, shape, internal echotexture parameters paying attention to the prospective and retrospective follow-up duration of the lesions to exclude malignancy. The absence of similar echogenicity to the mediastinal thymus and the increase in size in the last 1-year follow-up excluded the diagnosis of IET. Since the inability to select the contours suggests a pseudonodular appearance in autoimmune thyroid disorders rather than a true nodule, the relevant views were not included in the nodule class.

First of all, both thyroid nodules and IETs were evaluated on grayscale ultrasonography based on location, shape, size (<1cm, >1cm), echogenicity, volume, and internal echotexture. Echogenicity similar to the mediastinal thymus, geographic, longitudinal, or irregular shape along with internal tiny echogenicities were identical for IET. Solid appearance with spherical or ovoid shapes, having well-defined borders, presenting different echogenicities from mediastinal thymus were included in the thyroid nodule group. Since IETs are not reported as an indication for biopsy in the literature, none of the lesions were further evaluated according to cytopathological findings. Thyroid nodules were further classified according to the ACR TI-RADS system (10). We performed the fine-needle aspiration biopsy to the nodules that are in the category of TI-RADS 3 that are larger than 2.5 cm and in the category of TI-RADS 4 that are larger than 1.5 cm. Five nodules underwent fine-needle aspiration biopsy but no one had a diagnosis of malignancy or suspicion for malignancy. All patients were under follow-up at least 1-year without the development of a malignancy. We performed SMI and SWE evaluation of the thyroid nodules before the fine-needle aspiration biopsy.

Grayscale ultrasound, SWE, and SMI assessments were performed with the consensus of the pediatric radiologist (two years of SWE and SMI experience) and a radiologist having more than five years of ultrasound experience. The lesions compatible with a solid thyroid nodule or IET based on the radiological properties were enrolled. Images were

Figure 1. a) Grayscale ultrasound image of a 5-years-old male patient demonstrates aberrant ectopic cervical thymus (closed arrow) and ectopic thyroid tissue (open arrow) at the submandibular region along with internal jugular vein (blue circle) and carotid artery (red circle) in the same frame. The thymus is hypoechoic compared to the thyroid gland and includes tiny echogenic structures. b) Grayscale ultrasound image of an 8-years-old male patient's thyroid gland shows a longitudinal shaped and hypoechoic ectopic thymic tissue located posteriorly at the right thyroid lobe which is hypovascular compared to the surrounding thyroid tissue on SMI. c) A superb microvascular image of a 10-years-old male patient's thyroid gland reveals peripheral and intralésional hypervascularity of the thyroid nodule compared to the surrounding thyroid parenchyma which demonstrates the ring sign.

acquired with an ultrasound device using a 14-MHz linear array transducer (Aplio 500 Platinum, Canon, Japan) equipped with SWE and SMI application. Ultrasonographic evaluations were performed in a supine position with the neck in slight hyperextension. Patients were instructed to minimize swallowing and stay still during imaging. The linear probe surface was covered with a gel pad that was 3 mm in thickness. The longitudinal axis of the probe was perpendicular to the thyroid gland without any external compression. The thyroid nodules and IETs were evaluated in terms of shape, location, distribution, echogenicity, size, and vascularity. Three largest diameters of the lesions were measured and volumes (mL) (width (cm) length (cm) x height (cm) x 0.52) were calculated.

All SWE examinations were performed

using the thyroid preset and a linear transducer. The longitudinal and axial plans of the thyroid gland were demonstrated. Patients who represented full cooperation during imaging allowing real-time optimal propagation maps were included. When the probe was placed perpendicular to the skin and the inside of the selected box was completely color-coded and the propagation lines parallel to each other were observed, the optimal image that could be measured was accepted as obtained. Three regions of interest that were 3 mm in diameter were obtained on both axial and longitudinal plans by SWE within the borders of the nodules and IETs (Fig. 2, 3). Median stiffness values of six measurements of each lesion were calculated to reduce deviations and median values were recorded both as shear wave elasticity (SWE, kPa) and shear wave velocity (SWv, m/sec) values.

Both IETs and thyroid nodules were evaluated with color mode SMI. The frame rate and pulse repetition frequency values were set to 50 fps and 150-200 Mhz. Once the lesion was demonstrated with its largest section area on SMI, then the lesions were outlined manually on the color SMI images and vascularity index (VI) was calculated automatically as the ratio of colored pixels to all pixels in the outlined region of interest. Three different acquisitions were obtained and median VI values were noted. The median values of SWE and VI in the thyroid nodule and IET group were used for statistical purposes.

Statistical Analysis

Statistical analysis was performed using SPSS (version 21.0, IBM Corp.). The distribution of the data was evaluated by the Kolmogorov-Smirnov test. Age of the participants along with size, VI, and SWE parameters of the lesions was expressed as minimum, maximum, median, and range. Mann-Whitney U test was used to evaluate differences in the VI and SWE parameters between thyroid nodules and IETs. Spearman's correlation analysis was performed to evaluate the relationship between VI and SWE parameters. ROC curves were plotted to depict sensitivity, specificity, diagnostic accuracy, and predictive values of VI and SWE parameters in the differentiation of nodules from IETs.

RESULTS

Imaging characteristics of thyroid nodules and IETs in terms of location, echogenicity, size, and shape along with thyroid parenchymal echogenicity

were given in Tables 1 and 2. IETs were commonly located at the right thyroid lobe, posteriorly, and in the middle or lower aspect of the gland. Most of the IETs are hypoechogenic to the thyroid gland and shorter than 1 cm on the longest diameter. None of the patients with an IET had thyroid parenchymal disease on ultrasonography. Thyroid nodules were located commonly at the middle third of the thyroid gland. Most of the thyroid nodules were either hypoechogenic or isoechoic to the thyroid gland. Two thirds of the nodules were greater than 1 cm on the longest diameter. One of the thyroid nodules was taller than wider. None of the thyroid nodules included microcalcifications. The ACR TI-RADS category of the nodules was found between 3-5 with the most common TI-RADS 3 category. Thyroid parenchymal disease was depicted in 5 of 27 patients, of which 2 were dysshormonogenesis and 3 were autoimmune parenchymal diseases.

Descriptive statistics of the parameters are given in Table 3. The median ages of the cases were 15.6 (range: 10-18) years in the thyroid nodule group and 8.8 (range: 3-14) years in the IET group. There was a statistically significant difference between the median ages of the groups ($p < 0.001$). Children in the thyroid nodule group were older than in the IET group.

The median volumes of the thyroid nodules and IETs were 3.7 (range: 1.2-4.2) mL and 0.9 (range: 0.7-1.6) mL, respectively. There was a highly significant difference between the median volumes of the lesions ($p < 0.001$).

The median VI values of the nodules and IETs were 23.8 (range: 7.5-40) % and 4.7 (range: 0.2-16) %, respectively. Median VI values of the thyroid nodules were significantly higher than IETs ($p < 0.001$).

The median SWe values were 15.58 (range: 8.5-23.4) kPa and 7.6 (range: 4.4-9.5) kPa in the nodule and IET group, respectively. The median SWv values were 2.25 m/sec (range: 1.69-2.8 m/sec) and 1.64 m/sec (range: 1.23-1.83 m/sec) in the nodule and IET group, respectively. SWe and SWv parameters were significantly higher in the thyroid nodules compared to IETs ($p = 0.001$).

Correlation analysis results are given in Table 4. There was a mild positive correlation between VI values and the lesion volumes ($r = 0.34$, $p = 0.018$). There were significant moderate positive correlations between the SWE parameters with lesion volumes ($r = 0.46$ - 0.5 , $p = 0.001$). There were highly significant moderate positive correlations between the VI values and SWE parameters ($r = 0.64$ - 0.7 , $p = 0.001$). There were significant moderate positive correlations of VI and

SWE parameters with the age ($r = 0.64$ - 0.69 , $p = 0.001$).

ROC curves were plotted for differentiating thyroid nodules from IETs by SWE and SMI (Table 5, Fig. 4). When the VI cut-off value was set to 13%, the sensitivity, specificity, diagnostic accuracy, positive and negative predictive values were 88%, 95%, 91%, 95%, and 86%, respectively. When the SWe cut-off value was set to 9.2 kPa, sensitivity, specificity, diagnostic accuracy, positive and negative predictive values were 92%, 95%, 93%, 96%, and 90%, respectively. When the SWv cut-off value was set to 1.82 m/sec, sensitivity, specificity, diagnostic accuracy, positive and negative predictive values were 88%, 95%, 91%, 98%, and 83%, respectively.

DISCUSSION

Radiological imaging modalities play an important role in differentiating the thymic tissue. The Thymus tissue is bilobed and triangular in shape and hypodense to the thyroid gland on non-enhanced computed tomography because of the intense iodine content of the thyroid gland. Magnetic resonance imaging signal characteristics depend on the portion of the fatty replacement providing T1 and T2 weighted hyperintensity by age. The most preferred and initial imaging modality for diagnosing thymus tissue is that of ultrasound. Ultrasonographic appearances of both thymus tissue and also intrathyroidal thymic inclusions have been widely reported (11,12). Although the well-documented common locations, shape, echogenicity, and internal structures of IETs, these formations could be confused with the nodules in centers without enough experience. Therefore, we aimed to clarify the differentiation of IET from thyroid nodules with more advanced quantifications by recently developed imaging techniques. A comparative evaluation of IETs with thyroid nodules by SWE has not been published yet. This is the first article calculating the vascularity indices of IETs and thyroid nodules by SMI.

Thymus tissue has a soft consistency due to its imaging properties that extend in the compartments and do not displace the visceral organs. On the other hand, even if it is benign, thyroid nodules are formations with palpable stiffness that create a change in thyroid tissue location, compression effect, and capsule tension due to increased cellularity and vascularity. If these different elasticity properties can be demonstrated with reproducible measurements, beyond qualitative morphological features, IETs can be distinguished from nodules without histopathological evaluation by

Figure 2. A geographic shaped intrathyroidal ectopic thymus located posteriorly in the left thyroid lobe of a 7-years-old male patient. The lesion volume was 0.2 mL (a). Median SWE was 7.3 kPa (b), median VI was 5.8% (c).

Figure 3. A slightly hypoechoic solid thyroid nodule of an 11-years-old male patient. The nodule volume was 0.2 mL (a). Median SWE was 21.3 kPa (b), median VI was 40.5 % (c).

Figure 4. ROC curve was plotted for shear wave elasticity, shear wave velocity, and vascularity index values. Areas under the curves were all higher than 95% corresponding to highly significant diagnostic accuracies.

a comfortable and confident diagnostic method.

Normal thyroid gland elasticity by SWE between 8.8 kPa to 14.6 kPa has been documented in several studies (13,14). A diffusely enlarged hypoechoic gland with tiny echogenic reticulations could be found in thyroid dysmorphogenesis without significant change in tissue elasticity but increased vascularity (15). Vascularity features preclude elasticity properties in the diagnosis of dysmorphogenetic thyroid gland. Dysmorphogenetic thyroid tissue with reduced echogenicity and internal tiny echogenicities is found in the differential diagnosis of the ectopic cervical thymus. However, tiny internal echoes in the dysmorphogenesis tend to be reticular in shape but they have a punctate shape within a normal thymus gland (15,16).

There has been no previous study quantitatively evaluating thyroid nodules in children by SWE while there are only a limited number of studies evaluating

Table 1. Morphological findings of IET on grayscale ultrasonography

		Number (n)	Percent (%)
Laterality	Right	12	60
	Left	8	40
Anteroposterior distribution	Anterior	0	0
	Middle	4	20
	Posterior	16	80
Craniocaudal distributrion	Upper	0	0
	Middle	13	65
	Lower	7	35
Echogenicity	Hypoechoic	18	90
	Isoechoic	1	5
	Hyperechoic	1	5
Shape	Longitudinal	2	10
	Irregular	16	80
	Ovoid	2	10
Size	<1 cm	15	75
	>1 cm	5	25
Thyroid parenchymal disease	Present	0	0
	Absent	20	100

Table 2. Morphological findings of thyroid nodules on grayscale ultrasonography

		Number (n)	Percent (%)
Laterality	Right	16	59.2
	Left	11	40.7
	Anterior	8	29.6
Anteroposterior distribution	Middle	11	40.7
	Posterior	8	29.6
	Upper	2	7.4
Craniocaudal distributrion	Middle	17	62.9
	Lower	8	29.6
	Hypoechoic	12	44.4
Echogenicity	Isoechoic	13	48.1
	Hyperechoic	2	7.4
	<1 cm	18	66.7
Size	>1 cm	9	33.3
Taller than wider	Present	1	3.7
Microcalcification	Absent	27	100
	3	14	51.8
ACR TI-RADS category	4	10	37
	5	3	11
Thyroid parenchymal disease	Absent	22	81.5
	Present	5	18.5

Table 3. Descriptive statistics of the lesions regarding shear wave elastography parameters and vascularity index along with the age of the participants

		Minimum	Maximum	Median	Range	p
Age (years)	IET	3	14	8.8	11	0.001
	Nodule	10	18	15.6	8	
Volume (ml)	IET	0.7	1.6	0.9	0.9	0.001
	Nodule	1.2	4.2	3.7	3	
SWe (kPa)	IET	4.4	9.5	7.6	5.1	0.001
	Nodule	8.5	23.4	15.58	14.9	
SWv (m/sec)	IET	1.23	1.83	1.64	0.6	0.001
	Nodule	1.69	2.8	2.25	1.11	
VI (%)	IET	0.2	16	4.7	15.8	0.001
	Nodule	7.5	40	23.8	32.5	

p-values were obtained with the Mann-Whitney U test. IET: Intrathyroidal ectopic thymus, SWe: shear wave elasticity, SWv: shear wave velocity.

thyroid nodules in adults quantitatively by shear wave speed (17). On the other hand, many studies evaluating thyroid nodules with semi-quantitative scoring systems in the adult age groups either with SWE or strain elastography have been published. The current study is the first one evaluating the thyroid nodules quantitatively only in children by shear wave speed and also elasticity. In the current study handled benign and solid nodules, median elasticity values of the thyroid nodules were two times higher than normal thyroid elasticity reported in the literature and also the median elasticity of the IETs, which is the comparison group. The elasticity of the thyroid nodules by strain index has been investigated in comparison with thyroid parenchyma revealing a strain ratio lower than 2 suggesting follow-up; and the strain ratio greater than 5 recommended for a biopsy (18). The best cut-off SI value in differentiation of benign and malignant nodules has been depicted as 4.2 (18) and this has been found as 2.74 m/sec by point shear wave elastography (19). In the current study, median elasticity values of the benign thyroid nodules in children were 2.24 m/sec, which is compatible with the previous results of benign thyroid nodules in adults. The papillary thyroid carcinomas were evaluated within the malignant nodule group and expected to present a higher stiffness than 2.74 m/sec (19). Although papillary thyroid carcinoma with microcalcifications is shown in the differential diagnosis of IETs, further studies comparing the IETs and malignant thyroid nodules would confirm the easier and confident discrimination by tissue elasticity considering cut-off values since it is known that malignant nodules will show higher stiffness values. SWE would facilitate distinguishing both benign

and malign nodules from IETs and reduce unnecessary interventions by demonstrating stiffness values around 7 kPa and 1.64 m/sec for IETs.

Quantitative evaluation of thymic tissue has been assessed by SWE and strain elastography (9, 16). Mediastinal thymus stiffness in children by SWE has been found between 6.3 to 7.15 kPa and 1.45 to 1.53 m/sec decreasing after 5 years (16). The median stiffness values for intrathyroidal ectopic thymus were found to be 7.6 kPa and 1.64 m/sec in the current study, which was slightly higher than those depicted for mediastinal thymus (16). Given the depicted mean thyroid elasticity values, the relatively higher SWE value of thymic inclusion compared to the mediastinal thymus may be due to entrapment within the thyroid which is as relatively stiffer tissue than the thymus. A recent study investigating IET stiffness compared to surrounding thyroid parenchyma by strain elastography has revealed the strain index (SI) around SI: 0.95-1.09 (mean: 1.02) (9) concluding similar elasticity of IET with the thyroid gland. Although this study does not make a comparison of the thymic inclusion with the thyroid parenchyma in terms of elasticity, previous data revealed that thyroid tissue may exhibit similar or higher stiffness than thymic inclusion (9). Further studies are needed comparing the elasticity values of both intrathyroidal and also extrathyroidal aberrant thymus with thyroid tissue.

SMI is a novel ultrasonography application demonstrating low-velocity flow signals without direction data. Smaller vessels could be demonstrated with lower pulse repetition frequencies and higher frame rates by SMI due to the clutter suppression technique compared to power Doppler ultrasound. There have been recent studies concluding higher diagnostic accuracy of SMI compared to power Doppler by demonstrating healthy palatine tonsil (20) and parotid gland (21) parenchymal vascularity in children. VI has also a potential contribution in diagnosing pathological conditions such as thyroid dysmorphogenesis (15) compared to euthyroid glands and Graves disease (22) compared to Hashimoto's thyroiditis. SMI provides a novel quantitative Doppler index as "VI" which is the ratio of the number of the color pixels to the total pixels within the region of interest. Since IET has geographic

Table 4. Correlative analysis of age and volume with quantitative elasticity and vascularity parameters

	r	p
Volume - VI	0.34	0.018
Volume - SWe	0.5	0.001
Volume - SWv	0.46	0.001
VI - SWe	0.64	0.001
VI - SWv	0.70	0.001
Age - SWe	0.69	0.001
Age - SWv	0.64	0.001
Age - VI	0.67	0.001

p-value was obtained with Spearman's correlation analysis.

Table 5. ROC Curve analysis results

	AUC	p	Cut-off	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)	PPV(%)	NPV(%)
SWe (kPa)	0.98	0.001	9.2	92	95	93	96	90
SWv (m/sec)	0.96	0.001	1.82	88	95	91	98	83
VI (%)	0.97	0.001	13	88	95	91	95	86

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value.

contour, we depicted the VI values with the freehand technique by manually outlining contours of both IET and nodules. Doppler ultrasonography provides a valuable contribution in benign thyroid disorders such as autoimmune thyroid disorders, dyshormonogenesis, and thyroid nodules. As far as we know, there is no other study that quantitatively presents the vessel density of the thyroid nodules or IET tissue by VI values. Since thyroid nodules are hyperplastic lesions and IET is a parenchymal tissue, we demonstrated higher vascularity of nodules by vessel density on SMI. By qualitative evaluation, all IET lesions are hypovascular compared to the surrounding thyroid parenchyma and all nodules are hypervascular compared to the surrounding thyroid tissue in the current study. We clarified this qualitative finding with quantitative VI values. This rule may be impaired in comparison with dyshormonogenic gland and tissues with autoimmune thyroid disease. In our previous study, we demonstrated that the VI in the thyroid lobes was higher in patients diagnosed with Graves disease than those diagnosed with Hashimoto's thyroiditis and that the normal thyroid tissue VI was lower than those diagnosed with Hashimoto's thyroiditis (22).

The commonly used TI-RADS classification system does not evaluate nodule vascularity for categorization. However, recent studies demonstrated that combined evaluation of thyroid nodules by SMI (23) and contrast-enhanced ultrasound has increased the diagnostic accuracy of the TI-RADS classification system (24) especially in the TI-RADS 4 category compatible with intermediate malignancy risk in thyroid nodules. Recent studies documented scoring systems based on visual vascularity density by a semiquantitative evaluation method (25). As far as we know, this is the first study investigating the vascularity of IET and thyroid nodules with a quantitative novel parameter along with elastography. No comparable quantitative data regarding nodule or IET VI were available in the literature. The thyroid nodule VI seems to be similar to the parenchymal VI depicted in the Graves disease in a previous study and thyroid nodules presented higher VI compared to normal thyroid parenchyma and thyroid gland with Hashimoto's thyroiditis (22). Additionally, VI of IETs was found to be lower than the normal thyroid lobe VI depicted in the previous study (22). On Doppler ultrasound, complete surrounding peripheral microvasculature (ring sign) with homogeneity of branching has been reported (26) for benign nodules while only some nondisplaced vessels could be seen within an IET (5) in terms of comparison of nodules with IET vascularity by a qualitative approach.

IETs are commonly diagnosed in the first decade of childhood due to the differences in the echogenicity of the thyroid and thymus gland. Both intrathyroidal and also mediastinal thymus start to involute in terms of size and also echogenicity by transforming to hyperechogenic due to the fatty replacement after puberty. Therefore, it would be difficult to determine hyperechogenic thymic inclusion in the thyroid gland of older children and adults. This may explain the relatively lower median age values of the participants included in the IET group. On the other hand, thyroid nodules are mostly encountered in patients with autoimmune thyroid disorders in the second-decade followed by in presence of dyshormonogenesis depicted in the first decade. The mean age of the children with IET in a large study has been found as 7 years (6). On the other hand, 93% of the nodules in female children were found in children older than 11 years and 79% of the nodules in male children were found in children older than 13 years (27). For proper comparison with IETs, nodules detected in younger patients as possible are included. However, since most of the cases were accompanied by an autoimmune disease rather than dyshormonogenesis, the age of the patients included in the nodule group was higher than in the IETs group. Studies have reported that age is a parameter that positively correlates with tissue stiffness. In our correlation analysis, we found that stiffness and vascularity values increase with age. Therefore age differences may mildly contribute to higher stiffness in the nodule group compared to IETs.

When we consider the comparison in terms of size, it has been determined that IETs are smaller than nodules. 75% of the IETs and 66% of the benign thyroid nodules were smaller than 1 cm in our cohort. It has been demonstrated that the discriminatory efficiency of the quantitative assessment techniques we recommend is quite high even in lesions smaller than 1 cm. The mean longest diameter of the IET has been found to be 4.7 ± 3.3 mm (8) while aberrant cervical ectopic thymus tends to be larger than IET tissue (8). The parameters for size evaluation tend to be lower in IETs than expected for solid nodules. Therefore, nodules smaller than 1 cm should be quantitatively and carefully evaluated in detail before making a biopsy decision and IET would be kept in mind in geographic-shaped lesions smaller than 5 mm and 1 mL which are encountered in younger children.

This study has some limitations. First, the diagnosis of IET has been made due to the clearly described imaging features in the previous studies. Second, we did not subdivide the nodules either benign or malignant because in the current cohort any of the

nodules were malignant. Therefore, this study could not depict the diagnostic accuracy of these novel imaging modalities in terms of nodule classification. Third, we did not compare the results with papillary thyroid carcinomas as the differential diagnosis of IET. However, the vascularity and elastography parameters were extremely different among IET and nonspecified benign solid nodules. Fourth, we did not evaluate the surrounding thyroid parenchyma quantitatively. Finally, the study was a cross-sectional study, we could not provide quantitative data during the involutional process of the IET and also the biochemical status of the children in terms of thyroid functions.

In conclusion, differentiation of the nodules from IET would be feasible with SMI and SWE. Further investigation with these novel applications would reduce unnecessary interventions.

Conflict of interest

The authors declare that they have no conflict of interest. Ethical statements

All procedures were conducted in accordance with the ethical standards of The Ethics Committee of The Istanbul University, Istanbul Medical Faculty, and with the Helsinki Declaration. Informed consent was obtained from the patients.

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