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Should we reconsider high-risk features in thyroid ultrasonography?

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SUMMARY

OBJECTIVE: Round shape is generally considered to reduce the risk of malignancy according to recent guidelines. On the contrary, according to some reports, spherically shaped thyroid nodules are associated with a higher risk of malignancy. Thus, we aimed to evaluate the malignancy risk of solid round isoechoic nodules detected at thyroid ultrasonography and compare it with that of solid ovoid isoechoic nodules.

METHODS: Between 2017 and 2022, solitary solid round isoechoic nodules with diameters ³10 and £25 mm at thyroid ultrasonography were retrospectively selected and enrolled in the study. Age, size, nodule volume, serum thyrotropin levels, thyroid antibody levels, and cytopathological and histopathological results were recorded.

RESULTS: A total of 457 solitary solid isoechoechoic nodules from 457 patients (262 females and 195 males; median age, 59 [31–70] years) were selected, of which 203 were solid round isoechoic nodules, and 254 were solid ovoid isoechoic nodules. A total of 54 surgical operations were performed on 457 nodules, and 31 of them resulted in malignancy. From the 31 malignant results, 25 originated from solid round isoechoic nodules and the remaining 6 originated from solid ovoid isoechoic nodules ($p<0.025$).

CONCLUSION: We found that round nodules have higher malignancy rates than ovoid nodules. We think that ultrasonographic risk stratification systems used to target the most suitable nodules for the necessary biopsies can be dynamically updated, and sphericity can be added as a parameter in patient-based decision-making.

KEYWORDS: Thyroid nodule. Color doppler ultrasonography. Malignancy. Fine needle aspiration.

INTRODUCTION

Thyroid nodules are common in about 50% of the adult population with imaging modalities, and their frequency increases with the age of the population. The risk of malignancy ranges from 7 to 15%, depending on several risk factors[1]. Evaluation of thyroid nodules is mainly based on sonographic assessment and fine needle aspiration biopsy (FNAB). Several sonographic guidelines on thyroid imaging reporting and data systems (TIRADS) employ sonographic criteria to intensify the diagnostic workup and select the suspicious thyroid nodules for FNA. These systems try to establish a standard dictionary of nodule description, define the suspicious characteristics, put the nodule into a risk category, and identify those nodules in which FNA is indicated also by considering the size[2,3].

There are common high-risk sonographic features in different TIRADS, such as marked hypoechogenicity, irregular margins, punctuate echogenities, taller-than-wide shape, and evidence of extrathyroidal growth or pathologic lynphadenopathy. The highest diagnostic accuracy for predicting malignancy was taller-than-wide shape, which reflects a centrifugal pattern of growth[4-8]. Nevertheless, in sonographic classifications, isoechogenicity and round shape are usually among the features that do not affect the risk category of an individual nodule.

Recently, a large prospective cohort study reported that spherically shaped thyroid nodules are associated with a higher risk of malignancy irrespective of age, sex, and nodule size[9]. Thus, we aimed to report our institutional data on relatively small (i.e., 10–25 mm) round isoechoic nodules retrospectively, calculate their spherical shape configuration, and examine their association with malignancy.

METHODS

These retrospective cohort data were collected at our tertiary university hospital in Ankara, from January 2017 to June 2022. Solitary and solid thyroid nodules with the longest diameters of ≥10 and ≤25 mm detected at thyroid ultrasonography (US) were retrospectively selected and enrolled in the study. Age, sex,

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sonographic features, laboratory data, and cytopathological and/or histopathological results were recorded. The study was approved by the local Institutional Research Ethics Committee [Ankara University, 2022000054-1(2022/54)] and certified that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Thyroid ultrasonography, thyroid nodules, and fine needle aspiration biopsy

Thyroid ultrasonography was performed by 30 and 9-year experienced endocrinologists (MFE and AGC) using a Logiq S6 ultrasound system (GE® Healthcare, Milwaukee, WI) and a 10–13 mHz broadband linear probe. The length, width, and depth of each nodule were reported. The volume of each nodule was calculated using the ellipsoid formula (length×width×depth×π/6)[10]. Nodules were retrospectively classified as ovoid (solid ovoid isoechoic nodule [SOIN]) or round (solid round isoechoic nodule [SRIN]). We determined the round shape of a nodule when the ratio of anteroposterior diameter to either transverse or longitudinal diameter is between 0.9 and 1.1[11]. Oval shape is determined when the anteroposterior diameter of a nodule is less than its transverse diameter on the transverse and longitudinal planes[5]. Nodules with one or more highly suspicious US features (hypoechogenicity, irregular margins, punctuate echogenities, and taller-than-wide shape), hyperechoic/mildly or markedly hypoechoic nodules, and nodules with cystic components were excluded. Patients with a family history of any type of thyroid carcinoma and a history of head and neck irradiation were excluded. Ultrasonography-guided FNAB had been performed by using 22-gauge needles by those endocrinologists with nodules 1 cm or greater in maximal diameter because of the retrospective design of the study[10]. Results were described according to the Bethesda System for Reporting Thyroid Cytopathology[12]. Between 6 and 12 months, periodical sonographical follow-up was performed for all nodules, and repeated FNABs were performed if necessary. For cases of Bethesda 4, 5, and 6 results, the patients underwent either lobectomy or total thyroidectomy, and a subsequent surgical pathological diagnosis was reported[10]. A flow diagram is given for surgical decisions (Figure 1). The nodules that had at least two cytopathological diagnoses of Bethesda category 2 or when histopathological evaluation was benign were accepted as benign[9].

Laboratory evaluation

Serum thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-Tg) were examined. Normal ranges in our laboratory for TSH, fT3, fT4, anti-TPO, and anti-Tg levels are 0.38–5.33 mIU/mL, 3.99–6.71 pmol/L, 7–15.96 pmol/L, 0–9 IU/mL, and 10–115 IU/mL, respectively. Thyroid autoantibody positivity was determined as values higher than the reference.

Statistical analysis

The Kolmogorov-Smirnov criterion was used for the assessment of normality of diameters and volumes of thyroid nodules. Continuous variables were expressed as a mean±standard deviation or median (minimum and maximum). Discrete variables were expressed as medians with minimum and maximum values instead of interquartile ranges to demonstrate the heterogeneity of the data. Categorical variables, such as age and gender, were summarised as frequencies and percentages. For analysis of categorical variables, the chi-square test or Fisher exact tests were used. The SOIN and SRIN groups were compared with the Mann-Whitney U test for age and laboratory tests.

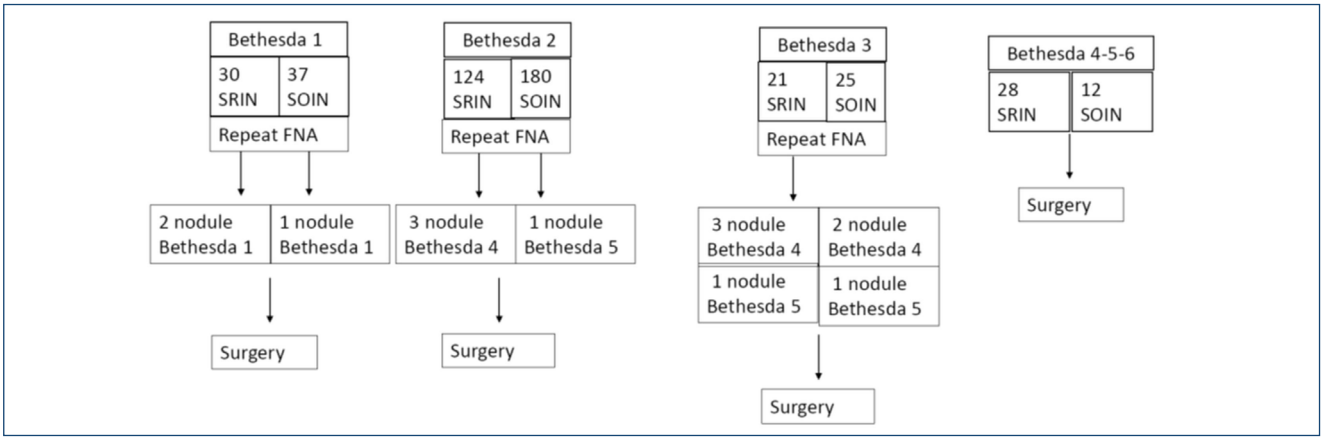

Figure 1. Flow diagram of selection of the nodules according to their Bethesda category for surgery. SRIN: solid round isoechoic nodule; SOIN: solid ovoid isoechoic nodule.

Statistical analyses were performed using the SPSS statistical software (released in 2015, IBM SPSS Statistics for Windows Version 23.0, IBM Corp., Armonk, NY). A two-tailed p<0.05 was determined as statistically significant.

RESULTS

A total of 457 solitary isoechoechoic nodules from 457 patients [262 females and 195 males; median age, 59 (31–70 years)] were selected for the present analysis. The median TSH was 1.16 (0.38–5.33) mIU/mL. The median largest diameter of nodules was 13 mm (10–25 mm), and the median total nodule volume was 0.83 (0.52–4.06) cm^3. In all, 203 of the nodules were SRINs, and 254 of them were SOINs. The median of age, largest diameter, nodule volume, TSH levels, and cytopathological (first fine needle aspiration) and histopathological results of SOINs and SRINs are given in Table 1. Repeated FNAB results were not included in the cytopathology section. Bethesda classes 2 and 6 were significantly different among SRIN and SOIN groups (p-value of 0.003 and 0.001, respectively).

It was observed that a total of 54 surgical operations were performed within 457 nodules, and 31 of them resulted in malignancy. Moreover, we found that out of 31 malignant results, 25 (80.6%) were SRINs and the remaining 6 (19.3%) were SOINs (p=0.025). Out of the 31 malignant nodules, 5 were compatible with follicular variant of papillary thyroid cancer (PTC) (diagnosed from four SRINs and one SOIN), and 26 were compatible with the classical type of PTC (diagnosed from 21 SRINs and 5 SOINs). Cytological distribution of the 31 nodules that were histopathologically proven to be malignant was as follows: 3 Bethesda class 1 (2 SRINs and 1 SOIN), 4 Bethesda class 2 (3 SRINs and 1 SOIN), 6 Bethesda class 3 (no SRIN and 6 SOINs), 4 Bethesda class 4 (4 SRINs and no SOINs), 3 Bethesda class 5 (1 SRIN and 2 SOINs), and 11 Bethesda class 6 (11 SRINs and no SOIN). Overall, Bethesda classifications were similar between the SRIN and SOIN groups. No laboratory or sonographic features could be detected to differentiate between the two groups (Table 2).

Thyroid autoantibody positivity (anti-TPO and/or anti-TG) was higher in SRINs than SOINs (p=0.03), but it was similar between malignant SRINs and malignant SOINs (p=0.94).

DISCUSSION

Several ultrasonographic high-risk features have been identified in the thyroid cancer risk assessment systems at present. Taller-than-wide shape has so far predicted a high risk of malignancy in the guidelines published for risk assessment[13]. Taller-than-wide configuration is reported to be specific but not

Table 1. Comparison of study parameters, and cytological (first fine needle aspiration) and pathological results of solid round isoechoic nodules and solid ovoid isoechoic nodules.

		SRIN (n=203)	SOIN (n=254)	p-value
Age (years)		55 (31–70)	61 (32–70)	**0.003**
Diameter (largest) mm		12 (10–25)	13 (10–25)	0.10
Nodule volume (cm^3)		1.08 (0.52–8.1)	0.70 (0.37–5.2)	**<0.001**
Serum TSH level (mIU/L)		1.2 (0.4–4.3)	1.15 (0.6–4)	0.24
Thyroid autoantibody positivity (anti-TPO and/or anti-TG)		42/203 (20%)	64/254 (25%)	**0.03**
Cytopathological results (initial)	Bethesda classification 1	30 (14.7%)	37 (14.5%)	0.057
	Bethesda classification 2	124 (61%)	180 (70.9%)	**0.003**
	Bethesda classification 3	21 (10.3%)	25 (10%)	0.358
	Bethesda classification 4	9 (4.4%)	10 (3.9%)	0.06
	Bethesda classification 5	8 (4%)	2 (0.8%)	1.000
	Bethesda classification 6	11 (5.4%)	0	**<0.001**
Not operated		166 (81.8%)	237 (93.3%)	0.05
Histopathological results	Malignant	25 (12.3%)	6 (2.4%)	**0.025**
	Benign	12 (5.9%)	11 (4.3%)	

TSH: thyroid stimulating hormone; TPO: thyroid peroxidase; Tg: thyroglobulin; AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasia; SFN: suspicious for follicular neoplasia; SM: suspicious for malignancy. Bold values indicate statistical significance at the p<0.05 level.

Table 2. The characteristics of the 31 histopathologically proven solid round isoechoic and solid ovoid isoechoic malignant nodules.

		SRINs (n=25)	SOINs (n=6)	p-value
Age (years)		52 (35–67)	44 (38–63)	0.300
Diameter (largest) mm		12 (10–24)	13 (11–25)	0.691
Nodule volume (cm^3)		0.93 (0.52–3.59)	2.2 (0.6–4)	0.249
Serum TSH level (mIU/L)		1.5 (0.52–4)	1.1 (0.5–2)	0.961
Thyroid autoantibody positivity (anti-TPO and/or anti-TG)		8 (32%)	2 (33%)	0.944
Cytological diagnosis	Bethesda 1	2	1	0.488
	Bethesda 2	3	1	1.000
	Bethesda 3	4	2	0.567
	Bethesda 4	4	0	0.561
	Bethesda 5	1	2	0.087
	Bethesda 6	11	0	0.065
Histopathological diagnosis	FV-PTC	4 (80%)	1 (20%)	1.000
	C-PTC	21 (80.7%)	5 (19.2%)	

TPO: thyroid peroxidase; TG: thyroglobulin; FV-PTC: follicular variant papillary thyroid carcinoma; C-PTC: classical type papillary thyroid carcinoma.

sensitive for malignancy with a false-negative rate of up to 40%[14]. Data have begun to accumulate, suggesting that the spherical shape may also pose a risk[9,11,15].

The growth of a malignant thyroid nodule depends on the sufficient supply of oxygen and nutrients provided by the vessels. Angiogenesis is a requirement for the invasion, progression, and metastasis of tumours[16]. Alexander et al., hypothesised that malignant tumours might configure their shape to maximise exposure and consumption of nutrients and growth. The spherical shape of a tumour maximises the surface area, enabling the maximum number of cells to receive nutrients. Alexander et al., reported that when nodules are classified according to long to short axis ratios (i.e., 1–1.49; 1.5–1.99; ≥2), spherical nodules have a substantially higher malignancy risk when compared to nonspherical ones[15]. Similar results were obtained by Kim et al., who reported that SRINs are associated with a relatively high malignancy rate of 25.9% (7 of 27 SRINs), regardless of their colour Doppler pattern[11]. Recently, in a large prospective study consisting of 4,282 nodules, authors argued that a system used to evaluate three dimensions in both axial and transverse planes is more appropriate than a cross-sectional ratio obtained from the transverse dimension alone. They reported that malignant nodules had a significantly lower long-to-short axis ratio than benign ones, indicating a greater risk of malignancy in more spherical nodules, and the risk continued to increase as the ratio approached a purely spherical ratio of 1.0 (i.e., >2.00, 14.6%; 1.51–2.00, 19.7%; 1.00–1.50, 25.5%; p<0.0001). Aside from the nodule's spherical shape, younger age and male sex were also independently correlated with the risk of cancer in multiple regression analysis, which may contribute to surgical decision-making for indeterminate cytological results[9].

On the contrary, an Italian group, using radiomics analysis of [^{18}F]-fluorodeoxyglucose-avid thyroid incidentalomas, reported that higher values of sphericity are associated with a lower risk of malignancy, with negative predictive values of 82% in a recent study. On the contrary, another Italian group, also using radiomics, reported that spherical configuration had a lower risk of malignancy in cytologically indeterminate thyroid nodules[17,18].

The association between chronic lymphocytic thyroiditis (CLT) and PTC has been investigated for several years. The biological association between CLT and differentiated thyroid cancer (DTC) has not been elucidated yet. In a meta-analysis, both positive thyroglobulin antibody (Tg) and positive thyroid peroxidase (TPO) antibody were found to be associated with an increased risk of DTC[19]. It was hypothesised that the exposure of thyroglobulin antigen during tumour formation could cause an increase in serum TgAb through immune responses[20]. On the contrary, there is an argument that lymphocytic infiltration developed mainly in response to the tumour itself, and lymphocytic infiltration represents a form of immune reaction to control tumour growth and proliferation[21]. In our study, a higher rate of anti-TPO/Tg positivity was obtained in SRINs than SOINs, but thyroid autoimmunity in histopathologically proven malignant nodules was similar between the SRINs and SOINs groups.

In this study, we report a significantly increased malignancy risk in SRIN group. A possible limitation of our study

is that the age was higher in the SOIN group than the SRIN group, but was similar between the SRIN-derived and SOIN-derived malignant populations (median age, 52 vs. 44 years). On the contrary, round nodules were strictly differed from ovoid ones by calculating three-dimensional ratios in the current study. In addition, nodules with cystic components and even those with slight hypoechogenicity or hyperechogenicity were excluded. Moreover, including relatively small- and medium-sized nodules (10–25 mm) in the study enables more precise measurements and avoids irregular-shaped nodules, which are usually more common among larger nodules.

CONCLUSION

We found that SRIN group have significantly higher malignancy rates than SOIN group, which contributed to Kim et al.'s initial findings. This supported the data that being in a round shape rather than ovoid alone poses an extra risk for malignancy in isoechoic nodules. Further studies with isoechogenicity and sphericity are needed to enable the addition of this easy-to-define, and reproducible feature to the risk stratification systems. Since thyroid nodules are quite common in daily practice and thyroid ultrasonography is an affordable, easy-to-use, and accessible technique, usual high-risk sonographic features should be constantly reviewed and revised to reveal a substantial impact on the evaluation of thyroid lesions.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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AUTHORS' CONTRIBUTIONS

AGC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Writing – original draft. **HYD:** Data curation, Investigation, Methodology. **FNK:** Data curation, Investigation, Methodology. **DGT:** Data curation, Investigation, Methodology. **MFE:** Project administration, Supervision, Writing – review & editing.

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