Re-Evaluation of 162 Malignant Thyroid Nodules that were Interpreted as Benign Based on Ultrasound Findings

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ABSTRACT

Purpose The goal of this study was to estimate the risk of malignant thyroid nodules being interpreted as benign based on ultrasound findings and to clarify the pathological features of these malignant nodules.

Materials and Methods We retrospectively re-evaluated ultrasound and pathological findings for 162 malignant thyroid nodules that were initially interpreted as benign based on ultrasound findings at Kuma Hospital between April 2012 and June 2015.

Results The incidences of malignancy among "benign" thyroid nodules were 0.5 % overall and 6.2 % among resected nodules. In addition, 82.7 % of thyroid nodules that were originally judged to have low or very low suspicion patterns were subsequently re-categorized as having high or intermediate suspicion patterns. The incidences of irregular margins (63.6 %) and low echogenicity (36.4 %) were higher than those of punctate microcalcification (17.9 %) and the taller-than-wide shape (20.4 %). Among microcarcinomas, the incidences were 65.7 % for irregular margins and 51.4 % for low echogenicity. Rim calcification with small extrusive soft tissue components and extrathyroidal extensions were not observed. After re-evaluation, 40.0 % of papillary thyroid carcinomas remained benign based on their variants, such as the encapsulated, follicular, macrofollicular, and oxyphilic cell variants.

Conclusion We conclude that more careful observation, especially for lesions with irregular margins and low echogenicity, can help improve the diagnostic accuracy of thyroid ultrasonography. Furthermore, greater care may decrease the incidence of malignancy among thyroid nodules with low or very low suspicion patterns. Some variants of papillary thyroid carcinoma can have benign ultrasound findings.

Introduction

Thyroid ultrasonography (US) is widely used to detect thyroid nodules and stratify their risk of malignancy (ROM). According to the 2015 American Thyroid Association guidelines for adult patients with thyroid nodules and differentiated thyroid cancer, the sonographic patterns of thyroid nodules are divided into five patterns (high suspicion, intermediate suspicion, low suspicion, very low suspicion, and benign) that have specific ROM values [1]. The low suspicion pattern involves an isoechoic or hyperechoic solid nodule or a partially cystic nodule with eccentric solid areas but no punctate microcalcification, irregular margins, extrathyroidal extension, or taller-than-wide shape. The estimated ROM for these lesions is 5–10 % [1–4] with malignancies generally involving the follicular variant (FV) of papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC) [5, 6]. However, no studies have performed a detailed examination of malignant nodules with benign

US findings. The present study aimed to estimate the ROM for thyroid nodules that were interpreted as benign based on ultrasound findings and to clarify the pathological features of these malignant nodules.

Materials and Methods

We reviewed 53,533 thyroid nodules that were evaluated using US at Kuma Hospital between April 2012 and June 2015. US was performed using the APLIO 80 SSA-770A system (Toshiba Medical Systems Co., Ltd., Otawara, Japan) or the APLIO 500 TUS-A500 (Toshiba) system with the PLT-805AT probe (5- and 12-MHz, Toshiba) or the PLT-1005BT probe (5- and 14-MHz, Toshiba). US examination and reporting was routinely performed by 14 clinical technologists, 12 of whom were registered medical sonographers certified by The Japan Society of Ultrasonics in Medicine. The US reports were interpreted based on the US classification (USC) proposed by Ito et al. (▶ **Table 1**) [4], with USC scores used to identify malignant lesions (3.5–5.0), borderline lesions (3), and benign lesions (2.0–2.5). For the present study, benign US findings in our classification included lesions with low or very low suspicion patterns based on the American Thyroid Association guidelines [1].

A total of 37,151 nodules (69.4 %) were initially considered benign (USC 2.0–2.5), including 2,804 nodules (7.5 %) that were surgically resected. Among the resected nodules, 173 nodules (6.2 %) were histologically confirmed to be malignant, which corresponded to an incidence of 0.5 % for malignancy among initially "benign" lesions. However, 11 of the 173 malignant thyroid nodules were excluded because internal echogenicity could not be observed. Therefore, we retrospectively re-evaluated the US findings for 162 malignant nodules that were originally interpreted as benign. The review was performed by one registered medical sonographer (T.F.).

When multiple thyroid nodules were present, they were evaluated separately. The potential US findings included taller-than-wide shape, margin status, echogenicity, punctate microcalcification, rim calcification with a small extrusive soft tissue component, and extrathyroidal extension. Taller-than-wide shape was defined as a ratio of ≥ 1 between the anteroposterior diameter and the transverse diameter. The patients' clinical data, US findings, and US images were obtained from their medical records. Pathological findings were reviewed using representative microscopic preparations. The statistical analyses were performed using Fisher's probability test, and differences were considered significant at p-values of < 0.05.

Results

▶ **Table 2** shows the re-evaluated US findings for the 162 malignant thyroid nodules, which included solid nodules (121 cases, 74.7 %; ▶ **Fig. 1a,b**), focally cystic solid nodules (37 cases, 22.8 %), and mainly cystic nodules (4 cases, 2.5 %; ▶ **Fig. 1c**). Hypoechoic results were observed for 59 nodules (36.4 %; 51 solid nodules, 7 focally cystic solid nodules, and 1 mainly cystic nodule), and irregular margins were observed for 103 nodules (63.6 %; ▶ **Fig. 1d**). These findings were also observed for 65.7 % of microcarcinomas (< 1.0 cm), and punctate microcalcifications were identified in 29 nodules (17.9 %; ▶ **Fig. 1e**), with a trend towards increasing frequency at larger sizes. A taller-than-wide shape was observed for 33 nodules (20.4 %; ▶ **Fig. 1f**), and the incidence was significantly higher in < 2.0 cm nodules than in > 2.0 cm nodules ($p = 0.0014$). We did not detect any cases with disrupted rim calcification, small extrusive hypoechoic soft tissue components, or extrathyroidal extension.

The histological diagnoses included PTC (146 nodules, 90.1 %), FTC (12 nodules, 7.4 %), poorly differentiated thyroid carcinoma (1 nodule, 0.6 %), medullary thyroid carcinoma (2 nodules, 1.2 %), and well differentiated carcinoma-not otherwise specified (1 nodule, 0.6 %). Among the 146 PTC nodules, 40 nodules (27.4 %) were variants, including the encapsulated variant (▶ **Fig. 2**), follicular vari-

▶ **Table 1** Ultrasonographic classification (USC) for thyroid nodules in Kuma Hospital and ATA guidelines.

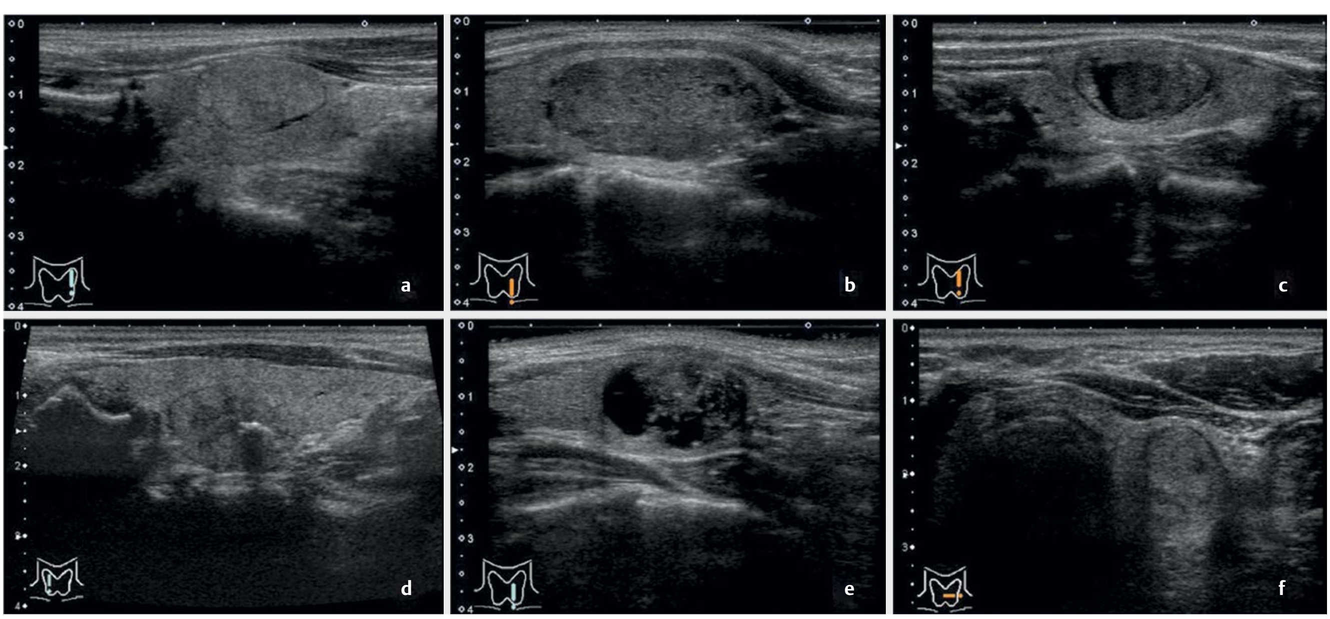
Kuma Hospital			ATA guidelines
USC *	**Description**	**Interpretation**	**Sonographic pattern**
1	Round or oval anechoic lesion	Benign	Benign
2	Regular-shaped nodule with cystic change. The echo level of the solid lesion is similar to that of normal thyroid	Benign	Very low suspicion
2.5	Nodule with cystic change, partially irregular shape and/or strong echoes internally or at the capsule	Benign	Low suspicion
3	Solid and regular-shaped nodule. Internal echo is homogeneous or may have strong echoes internally or at the capsule	Borderline	Intermediate suspicion
3.5	Solid nodule with focally irregular shape	Malignant	High suspicion
4	Solid and irregular-shaped nodule. Internal echo is usually low and may have fine strong echoes internally	Malignant	High suspicion
4.5	Solid and irregular-shaped nodule with minor extrathyroidal extension	Malignant	High suspicion
5	Solid and irregular-shaped nodule with extrathyroidal extension	Malignant	High suspicion

* Markedly calcified nodules are not evaluated.

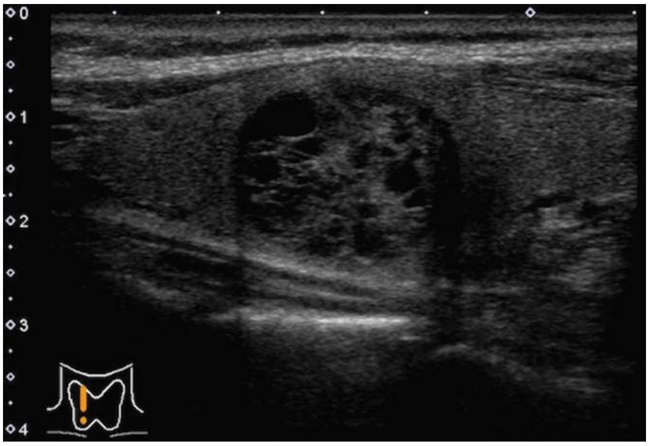
▶ **Table 2** Re-evaluated ultrasound findings for 162 malignant thyroid nodules that were interpreted as benign based on ultrasound findings.

	Total N = 162	Low echogenicity N = 59 (36.4 %)	Irregular margins N = 103 (63.6 %)	Punctate microcalcification N = 29 (17.9 %)	T/W ≥ 1 N = 33 (20.4 %)	Invasiveness## N = 0
Size						
< 10 mm	35	18 (51.4 %)	23 (65.7 %)	4 (11.4 %)	11 (31.4 %)	0
10–20 mm	75	29 (38.7 %)	51 (68.0 %)	14 (18.7 %)	19 (25.3 %)	0
20–40 mm	32	6 (18.8 %)	19 (59.4 %)	6 (18.8 %)	2 (6.3 %)	0
≥ 40 mm	20	6 (30.0 %)	10 (50.0 %)	5 (25.0 %)	1 (5.0 %)	0
Histology						
PTC	146 (90.1 %)	51 (34.9 %)	94 (64.4 %)	27 (18.5 %)	31 (21.2 %)	0
Classic	106 (72.6 %)	46	82	20	24	0
Encapsulated V#	25 (17.1 %)	2	14	7	4	0
Follicular V#	11 (7.5 %)	1	6	1	1	0
Macrofollicular V#	7 (4.8 %)	0	5	0	1	0
Cribriform V	3 (2.1 %)	2	0	0	1	0
Tall cell V	1 (0.7 %)	0	0	0	1	0
Oxyphilic cell V	1 (0.7 %)	0	0	0	0	0
FTC	12 (7.4 %)	6 (50.0 %)	7 (58.3 %)	1 (8.3 %)	2 (16.7 %)	0
Minimally invasive	7 (58.3 %)	4	3	1	1	0
Widely invasive	5 (41.7 %)	2	4	0	1	0
PDTC	1 (0.6 %)	0	1 (100 %)	0	0	0
MTC	2 (1.2 %)	2 (100 %)	1 (50.0 %)	1 (50.0 %)	0	0
WDC-NOS	1 (0.6 %)	0	0	0	0	0

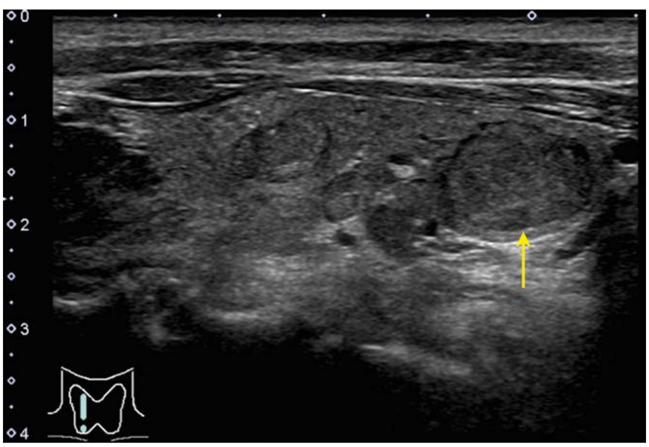
#: overlapping, V: variant, ##: rim calcifications with a small extrusive soft tissue component and extrathyroidal extension; T/W: taller-than-wide shape, PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, PDTC: poorly differentiated thyroid carcinoma, MTC: medullary thyroid carcinoma, WDC-NOS: well differentiated carcinoma-not otherwise specified.



▶ **Fig. 1** Ultrasound findings for malignant thyroid nodules that were originally interpreted as benign based on ultrasound findings. **a** Solid isoechoic nodule. **b** Solid hypoechoic nodule. **c** Cystic nodule. **d** Irregular margin. **e** Punctate microcalcifications. **f** Taller-than-wide shape (**a-e** : B-mode, longitudinal view, **f** : B-mode, transverse view).



▶ **Fig. 2** Papillary carcinoma, encapsulated variant. The mixed solid and cystic nodule was round and well-defined, with no punctate microcalcification (B-mode, longitudinal view).



▶ **Fig. 3** Papillary carcinoma, encapsulated and follicular variant. The isoechoic solid nodule (arrow) is surrounded by a low echoic rim (B-mode, longitudinal view).

▶ **Fig. 4** Papillary carcinoma, encapsulated and macrofollicular variant. The isoechoic solid nodule contains a focal cystic lesion without invasiveness or punctate microcalcification (B-mode, longitudinal view).

ant (FV; ▶ **Fig. 3**), macrofollicular variant (▶ **Fig. 4**), and the cribriform, tall cell, and oxyphilic cell variants. In two medullary thyroid carcinoma cases, the calcitonin levels of both the serum and needle wash-out fluids during aspiration were increased.

▶ **Table 3** shows that 134 nodules (82.7 %) were re-categorized into patterns with higher ROMs (high suspicion: 119 nodules [73.5 %], intermediate suspicion: 15 nodules [9.3 %]). The nodules' size did not affect this re-categorization. Low suspicion and very low suspicion patterns were observed for 16 nodules (9.9 %) and 12 nodules (7.4 %), respectively, with higher incidences observed for larger nodules than for smaller nodules.

Aspiration cytology revealed that 128 nodules (79.0 %) had suspected or confirmed malignancy. Among the 14 nodules that were reported to be benign, 8 nodules (57.1 %) were re-classified into the high suspicious pattern. Among the 28 nodules that still had low or very low suspicion patterns, 17 nodules (60.7 %) were diagnosed with suspected or confirmed malignancy based on aspiration cytology.

Among the 25 PTC nodules that were still considered benign after the re-evaluation, 10 nodules (40.0 %) were variants, including the encapsulated, follicular, macrofollicular, and oxyphilic cell variants. Two FTC cases with low or very low suspicion patterns after the re-evaluation were minimally and widely invasive FTC, respectively. In the latter case, the satellite nodules were originally interpreted as a benign nodular goiter (▶ **Fig. 5**).

Discussion

US is the most important imaging modality for evaluating thyroid nodules, and the American Thyroid Association guidelines [1] classify the US findings into five patterns: high suspicion, intermediate suspicion, low suspicion, very low suspicion, and benign. Each category has an estimated ROM and the indication for FNAC is determined based on the pattern and tumor size. Thus, the US-based categorization of thyroid nodules plays an important role in a patient's clinical management.

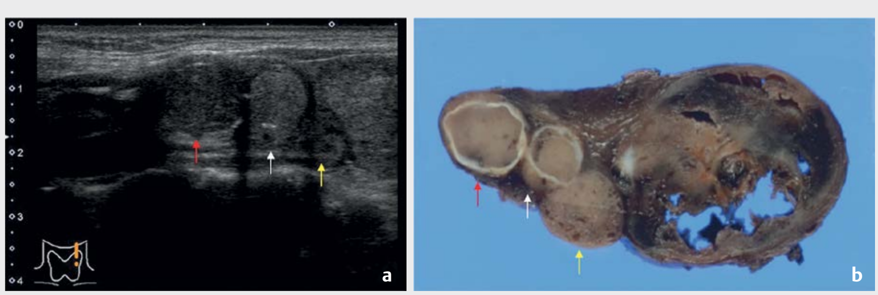
This retrospective study evaluated US findings for 162 thyroid nodules that had been interpreted as benign based on US findings but were subsequently confirmed to be malignant based on histological examination. The reported ROMs for low and very low suspicion patterns are 5–10 % and < 3 %, respectively [1, 7, 8], although the present study revealed ROMs of 0.5 % among all cases and 6.2 % among cases that involved resection. Nevertheless, differences in the diagnostic criteria, US classification, and study selection criteria preclude a head-to-head comparison of the ROM values.

The present study revealed that 82.7 % of thyroid nodules with initially low or very low suspicion patterns were subsequently re-categorized as having high or intermediate suspicion patterns based on the presence of more than one of the following: hypoechoic solid mass, irregular margins, punctate microcalcification, and a taller-than-wide shape [9–12]. Interestingly, irregular margins (63.6 %) and low echogenicity (36.4 %) were more common than punctate microcalcification (17.9 %) and taller-than-wide shape (20.4 %), and the former findings were even common for microcarcinomas (65.7 % and 51.4 %, respectively). However, we did not detect rim calcification with a small extrusive soft tissue component and extrathyroidal extension. The under-interpretation

▶ **Table 3** Re-evaluated ultrasound patterns for 162 malignant thyroid nodules that were interpreted as benign based on ultrasound findings.

	Total N = 162	High N = 119 (73.5 %)	Intermediate N = 15 (9.3 %)	Low N = 16 (9.9 %)	Very low N = 12 (7.4 %)
Size					
< 10 mm	35	26 (74.3 %)	6 (17.1 %)	2 (5.7 %)	1 (2.9 %)
10–20 mm	75	60 (80.0 %)	5 (6.7 %)	8 (10.7 %)	2 (2.7 %)
20–40 mm	32	21 (65.6 %)	2 (6.3 %)	3 (9.4 %)	6 (18.8 %)
≥ 40 mm	20	12 (60.0 %)	2 (10.0 %)	3 (15.0 %)	3 (15.0 %)
Cytology					
ND/UNS	1	0	0	1 (100 %)	0
Benign	14	8 (57.1 %)	0	4 (28.6 %)	2 (14.3 %)
AUS	13	8 (61.5 %)	2 (15.4 %)	1 (7.7 %)	2 (15.4 %)
Follicular neoplasm	6	4 (66.7 %)	1 (16.7 %)	0	1 (16.7 %)
Suspected malignancy	22	16 (72.7 %)	0	4 (18.2 %)	2
Malignant	106	83 (78.3 %)	12 (11.3 %)	6 (5.7 %)	5 (4.7 %)
Histology					
PTC	146 (90.1 %)	108 (74.0 %)	13 (8.9 %)	15 (10.3 %)	10 (6.9 %)
Classic	106	82	9	8	7
Encapsulated V#	25	18	1	3	3
Follicular V#	11	7	1	3	0
Macrofollicular V#	7	5	0	1	1
Cribriform V	3	1	2	0	0
Tall cell V	1	1	0	0	0
Oxyphilic cell V	1	0	0	1	0
FTC	12 (7.4 %)	8 (66.7 %)	2 (16.7 %)	1 (8.3 %)	1 (8.3 %)
Minimally invasive	7	4	2	1	0
Widely invasive	5	4	0	0	1
PDTC	1 (0.6 %)	1 (100 %)	0	0	0
MTC	2 (1.2 %)	2 (100 %)	0	0	0
WDC-NOS	1 (0.6 %)	0	0	0	1 (100 %)

#: overlapping, ND/UNS: nondiagnostic or unsatisfactory, AUS: atypia of undetermined significance, V: variant, PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, PDTC: poorly differentiated thyroid carcinoma, MTC: medullary thyroid carcinoma, WDC-NOS: well differentiated carcinoma-not otherwise specified.



▶ **Fig. 5** Widely invasive follicular thyroid carcinoma. Satellite nodules (red, yellow, and white arrows) were interpreted as a benign nodular goiter (**a** B-mode, longitudinal view, **b** cut surface).

might be related to inter-observer variability or different diagnostic criteria of US classification. In addition, we might have overlooked the findings suspecting malignancy or tended to avoid over-diagnosis in routine examination.

Inter-observer variability in the sonographic evaluation of thyroid nodules has been frequently discussed [13, 14], with low agreement values observed for subjective and qualitative findings, such as irregular margins and low echogenicity [13–15]. These features were frequently detected among malignant thyroid nodules that were originally interpreted as benign. In contrast, the present study less frequently detected more objective findings (e. g., punctate microcalcification and the taller-than-wide shape) and more easily recognizable findings (rim calcification with a small extrusive soft tissue component and extrathyroidal extension). Therefore, we conclude that more careful observation, especially in cases with irregular margins and low echogenicity, will further improve the diagnostic accuracy of thyroid US and decrease the incidences of thyroid nodules with low or very low suspicion patterns. It is also important to be aware that findings suggestive of malignancy can even be detected for microcarcinomas.

It has been reported that malignancy mainly involves FV-PTC and FTC for nodules with a low suspicion pattern [5, 6]. We have also reported that US findings of cribriform variant of PTC are similar to those of a follicular tumor or a nodular goiter [16]. The present study also revealed that 40 % of PTC nodules still had benign ultrasound findings after their re-evaluation, which involved the encapsulated, follicular, macrofollicular, or oxyphilic cell variants. It is also important to be aware that the satellite nodules of widely invasive FTC may be confused with an adenomatous goiter.

US elastography is an emerging technique that reflects the stiffness of the lesion and could be helpful for identifying nodules with an increased risk for malignancy [17–20]. Recently, it has also been reported that semiquantitative elastosonography is a valuable tool in the characterization of thyroid nodules and seems to be more sensitive than contrast-enhanced ultrasound [21–24]. However, we have not performed this technique in routine examinations. Therefore, we are unable to include data concerning US elastography in this study. The new techniques are not popular in Japan. We expect that under-interpretation will decrease by using such techniques in the future.

Conflict of Interest

The authors declare no conflict of interest.

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