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Impact of Nodule Size on Malignancy Risk Differs according to the Ultrasonography Pattern of Thyroid Nodules

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Objective: To test whether the impact of thyroid-nodule size on the malignancy risk differs according to the ultrasonography (US) patterns of nodules.

Materials and Methods: This study is a post hoc analysis using data from the Thyroid Imaging Reporting and Data System (TIRADS) multicenter retrospective study which included 2000 consecutive thyroid nodules (≥ 1 cm) with final diagnoses. A total of 2000 consecutive thyroid nodules from 1802 patients (1387 women and 613 men; mean age, 51.2 ± 12.2 years) were enrolled in this study. The malignancy risk of the nodules was assessed according to the nodule size and US patterns (Korean-TIRADS).

Results: Overall, the malignancy risk did not increase as nodules enlarged. In high-suspicion nodules, the malignancy rate had no association with nodule size (p = 0.467), whereas in intermediate- or low-suspicion nodules there was a trend toward an increasing malignancy risk as the nodule size increased (p = 0.004 and 0.002, respectively). The malignancy rate of large nodules (≥ 3 cm) was higher than that of small nodules (< 3 cm) in intermediate-suspicion nodules (40.3% vs. 22.6%, respectively; p = 0.001) and low-suspicion nodules (11.3% vs. 7.0%, respectively; p = 0.035). There was a trend toward a decreasing risk and proportion of papillary carcinoma and an increasing risk and proportion of follicular carcinoma or other malignant tumors as nodule size increased (p < 0.001, respectively).

Conclusion: The impact of nodule size on the malignancy risk differed according to the US pattern. A large nodule size (≥ 3 cm) showed a higher malignancy risk than smaller nodules in intermediate- and low-suspicion nodules.

Keywords: *Thyroid; Thyroid nodule; Thyroid malignancy; Ultrasonography; Tumor size; Nodule size; Risk of malignancy; Malignancy risk; Pattern analysis; Imaging analysis; Imaging pattern; Imaging feature*

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INTRODUCTION

The primary tumor size of thyroid cancer has been regarded as an important prognostic factor (1, 2). Therefore, large nodules are considered candidates for fine-needle aspiration (FNA) to screen for malignancy (3-5) . However, it remains controversial as to whether a large nodule size has a higher malignancy risk than smaller nodules. Several studies (6-8) have reported that nodule size may aid evaluation of the cancer risk, and that large nodules

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Korean Journal of Radiology
KJR

(> 3 or 4 cm) have a higher malignancy risk. Conversely, other studies reported that increased nodule size was not associated with an increased malignancy risk (9-12).

A recent study (6) reported that the proportion of papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC) among malignancies differed according to nodule size, which suggests that a change in the proportion of malignant tumor types might be related to a change in the malignancy risk as nodules enlarge (6). Because PTC and FTC have different ultrasonography (US) features (13, 14), the US patterns of tumors provide information on the histologic type of malignancy. Although many studies (6-12) have shown conflicting results regarding the association of nodule size and malignancy risk, the association of nodule size and malignancy risk according to US patterns has not previously been investigated.

The objective of this study was to test whether the impact of nodule size on the malignancy risk differs according to the US patterns in thyroid nodules.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board. The requirement for informed consent was waived due to the retrospective nature of the study.

Study Population

This study is a post hoc analysis using data from the Thyroid Imaging Reporting and Data System (TIRADS) multicenter retrospective study, which included 2000 consecutive patients with thyroid nodules (≥ 1 cm) who underwent FNA or core-needle biopsies (CNB) at four institutions (two primary medical centers and two tertiary hospitals) from January 2010 to May 2011 (15). A total of 2000 consecutive thyroid nodules from 1802 patients (1387 women and 613 men; mean age, 51.2 ± 12.2 years) were included in this study. A final diagnosis of malignancy was based on surgical pathology, except for lymphomas. Final diagnoses of benign nodules were determined by 1) histopathological diagnosis from surgical resections, 2) at least two benign diagnoses on FNA or CNB, and 3) an initial benign result for FNA or CNB nodules with a stable or decreased size after at least 12 months of follow-up US.

US Examination and Image Analysis

A high-resolution US scan using a 10–12 MHz or 5–14 MHz linear-array transducer (AplioXG, Toshiba, Otawarashi, Japan; iU22, Philips Medical Systems, Bothell, WA, USA) was performed. US images were retrospectively reviewed by one of three experienced radiologists (who had 19, 16, and 12 years of experience in performing thyroid US and interventional procedures, respectively). They were unaware of the FNA results or final diagnoses, and assessed the following US features of thyroid nodules: internal content, echogenicity, margin, shape, calcification, spongiform appearance, and comet-tail artifact. The thyroid nodules were categorized into four categories (benign, low-suspicion, intermediate-suspicion, and high-suspicion) using the Korean-TIRADS (K-TIRADS) (5). The high-suspicion (K-TIRADS 5) nodules include solid hypoechoic nodules with any suspicious US feature (microcalcification, non-parallel orientation, spiculated/microlobulated margin). The intermediate-suspicion (K TIRADS 4) nodules include solid hypoechoic nodules with no suspicious US feature and partially cystic or isohyperechoic nodules with any suspicious US feature. The low-suspicion (K-TIRADS 3) nodules include partially cystic or isohyperechoic nodules with no suspicious US feature. The benign (K-TIRADS 2) nodules include pure cysts, partially cystic with comet-tail artifacts, and spongiform nodules.

US-Guided FNA and CNB Procedures

Fine-needle aspiration was performed using a conventional method, and at least two samples were taken per nodule (16). CNB was performed using a disposable 18-gauge, single- or double-action spring-activated needle (TSK Acecut or Stericut, Create Medic, Yokohama, Japan), as described elsewhere (17). FNA was routinely performed for thyroid nodules > 1 cm, with the exception of pure cystic nodules, partially cystic nodules with comet-tail artifacts, and spongiform nodules. The interpretation of FNA was based on the Bethesda system for reporting thyroid cytopathology (18) and CNB results were diagnosed with a six-tier pathology reporting system (17, 19).

Data Analysis and Statistics

The unpaired *t* test was used to compare the mean nodule size between benign and malignant nodules. The nodule size was classified into 3 categories: 1–1.9 cm, 2–2.9 cm, and ≥ 3 cm. The chi-square test or Fisher's exact test was used to compare the risk of malignancy overall and according to the size of the nodules in each subgroup, categorized according to the US patterns. The chi-square test or Fisher's exact test was also used to compare the US patterns

among histologic types of malignancy, and to compare the malignancy risk and proportion of each histologic type of malignancy overall, and according to each subgroup of nodules categorized according to the US patterns. The chi-square test for trend was used to investigate the trend of the malignancy risk as the nodule size increased, and to assess the trend of the risk and proportion of the histologic types of malignant tumors as the nodule size increased. Statistical analyses were performed with IBM SPSS Statistics for Windows ver. 23.0 (IBM Corp., Armonk, NY, USA). A significant difference was defined as a p value of < 0.05.

RESULTS

Demographic Data

The maximal size of the nodules ranged from 10–100 mm (mean size, 20.0 ± 11.4 mm; median size, 16.0 mm). The mean size of benign nodules was slightly larger than that of malignant tumors (20.3 mm vs. 18.7 mm; p = 0.008). The final diagnoses of the 2000 nodules were 1546 (77.3%) benign nodules (1469 benign non-neoplastic nodules, 77 benign tumors) and 454 (22.7%) malignant nodules. Final diagnoses of malignant tumors were made by surgical resection in 451 (99.3%) and by CNB in three (0.7%) cases of lymphoma. Of the 454 malignant tumors, there were 388 (85.5%) PTC, 48 (10.6%) FTC, and 18 (4%) other malignant tumors including 7 medullary carcinomas, 5 lymphomas, 4 undifferentiated carcinomas, 1 squamous carcinoma, and 1 metastatic tumor.

US Patterns of Malignant Tumors

Table 1 shows the US patterns of PTC, FTC, and other malignant tumors. Malignancy was not found in nodules with a benign US pattern (K-TIRADS 2). The US patterns were significantly different between each histologic type of malignant tumor ($p \leq 0.02$). The most common US pattern of PTC was a high-suspicion US pattern, and there was a trend toward an increased frequency of PTC with an increased degree of suspicion US pattern ($p < 0.001$). PTC showed a high- or intermediate-suspicion US pattern in 83% of cases (322/388), FTC showed an intermediate- or low-suspicion US pattern in 89.6% (43/48), and other malignant tumors showed a high- or intermediate-suspicion US pattern in 94.4% (17/18). Among malignant tumors, the proportion of non-PTC malignant tumors including FTC and other malignant tumors was 5.2% in high-suspicion nodules, 24.1% in intermediate-suspicion nodules, and 25% in low-suspicion nodules.

Risk of Malignancy according to Nodule Size and US Pattern

Table 2 shows the malignancy risk of thyroid nodules according to nodule size both overall and among the subgroups based on the US patterns. Overall, there was no trend toward an increasing risk of malignancy as nodules enlarged (p = 0.544), and there was no significant difference in the malignancy risk between nodules < 3 cm and nodules ≥ 3 cm (22.9% and 21.6%, respectively; p = 0.569). However, thyroid nodules smaller than 2 cm showed a slightly higher malignancy risk than nodules larger than 2 cm (24.3% and 19.9%, respectively; p = 0.024).

In nodules with a high-suspicion US pattern, there was no significant association between the malignancy risk and nodule size (p = 0.467). However, there was a trend toward an increased malignancy risk as the nodule size increased in nodules with intermediate- and low-suspicion US patterns (p = 0.004 and 0.022, respectively). The malignancy risk of nodules ≥ 3 cm was significantly higher than that of nodules < 3 cm in intermediate-suspicion nodules (40.3% vs. 22.6%, respectively; p = 0.001) and low-suspicion nodules (11.3% vs. 7.0%, respectively; p = 0.035). There was no significant difference in the malignancy risk between nodules ≥ 2 cm and nodules < 2 cm in intermediate- and low-suspicion nodules (p = 0.808 and 0.328, respectively).

Table 1. US Patterns of Malignant Tumors

US Pattern (K-TIRADS)	No. of Malignant Tumors (%)	No. of Papillary Carcinoma (%)	No. of Follicular Carcinoma (%)	No. of Other Malignant Tumors (%)
All	454	388	48	18
High suspicion (K-TRIADS 5)	233 (51.3)	221 (57.0)	5 (10.4)	7 (38.9)
Intermediate suspicion (K-TIRADS 4)	133 (29.3)	101 (26.0)	22 (45.8)	10 (55.6)
Low suspicion (K-TIRADS 3)	88 (19.4)	66 (17.0)	21 (43.8)	1 (5.6)

Numbers in parentheses are percentages and indicate proportion of US patterns in each malignant tumor. K-TIRADS = Korean-Thyroid Imaging Reporting and Data System, US = ultrasonography

Korean Journal of Radiology
KJR

Malignancy Risk of Each Histologic Type according to Nodule Size and US Pattern

Table 2 shows the malignancy risk of each histologic type according to nodule size both overall and for each subgroup based on US patterns. There was a trend toward a decreasing risk of PTC and an increasing risk of FTC and other malignant tumors as the nodule size increased (p < 0.001, respectively). Although the risk of PTC was higher in nodules < 2 cm compared to nodules ≥ 2 cm (p < 0.001), the risk of FTC and other malignant tumors was higher in nodules ≥ 2 cm compared to nodules < 2 cm (p < 0.001, respectively). There was no significant difference in the risk of each histologic type of malignancy between nodules with a size of 2–2.9 cm and nodules ≥ 3 cm (p ≥ 0.054).

In nodules with a high-suspicion US pattern, there was no significant difference in the risk of PTC and non-PTC malignant tumors according to nodule size (p = 0.232 and p = 0.327, respectively). Large nodules, ≥ 3 cm, showed a 9.1% decrease in the PTC risk, 11% increase in the non-PTC malignancy risk, and 1.9% increase in the overall malignancy risk compared with nodules < 3 cm.

In nodules with an intermediate-suspicion US pattern, there was no significant difference in the risk of PTC according to nodule size (p = 0.142). However, there was a trend toward an increasing risk of FTC and other malignant tumors as the nodule size increased (p < 0.001,

Table 2. Risk of Malignancy and Distribution of Histologic Type according to Nodule Size and US Patterns

Size of Nodules	No. of Nodules	No. of Malignant Tumors (%)	Papillary Carcinoma		Follicular Carcinoma		Other Malignant Tumor	
			No. of Tumors (%)*	Proportion (%)†	No. of Tumors (%)*	Proportion (%)†	No. of Tumors (%)*	Proportion (%)
All‡	2000	454 (22.7)	388 (19.4)	85.5	48 (2.4)	10.6	18 (0.9)	4.0
1–1.9 cm	1285	312 (24.3)	296 (23.0)	94.9	12 (0.9)	3.8	4 (0.3)	1.3
2–2.9 cm	386	71 (18.4)	52 (13.5)	73.2	15 (3.9)	21.1	4 (1.0)	5.6
≥ 3 cm	329	71 (21.6)	40 (12.2)	56.3	21 (6.4)	29.6	10 (3.0)	14.1
1–2.9 cm	1671	383 (22.9)	348 (20.8)	90.9	27 (1.6)	7.0	8 (0.5)	2.0
High suspicion (K-TRIADS 5) on US								
All	294	233 (79.3)	221 (75.2)	94.8	5 (1.7)	2.1	7 (2.4)	3.0
1–1.9 cm	234	188 (80.3)	181 (77.4)	96.3	3 (1.3)	1.6	4 (1.7)	2.1
2–2.9 cm	39	28 (71.8)	26 (66.7)	92.9	0 (0.0)	0.0	2 (5.1)	7.1
≥ 3 cm	21	17 (81.0)	14 (66.7)	82.4	2 (9.5)	11.8	1 (4.8)	5.9
1–2.9 cm	273	216 (79.1)	207 (75.8)	95.8	3 (1.1)	1.4	6 (2.2)	2.8
Intermediate suspicion§ (K-TRIADS 4) on US								
All	533	133 (25.0)	101 (18.9)	75.9	22 (4.1)	16.5	10 (1.9)	7.5
1–1.9 cm	363	81 (22.3)	77 (21.2)	95.1	4 (1.1)	4.9	0 (0.0)	0.0
2–2.9 cm	98	23 (23.5)	13 (13.3)	56.5	8 (8.2)	34.8	2 (2.0)	8.7
≥ 3 cm	72	29 (40.3)	11 (15.3)	37.9	10 (13.9)	34.5	8 (11.1)	27.6
1–2.9 cm	461	104 (22.6)	90 (19.5)	86.5	12 (2.6)	11.5	2 (0.4)	1.9
Low suspicion‖ (K-TRIADS 3) on US								
All	1120	88 (7.9)	66 (5.9)	75.0	21 (1.9)	23.9	1 (0.1)	1.1
1–1.9 cm	660	43 (6.5)	38 (5.8)	88.4	5 (0.8)	11.6	0 (0.0)	0.0
2–2.9 cm	238	20 (8.4)	13 (5.5)	65.0	7 (2.9)	35.0	0 (0.0)	0.0
≥ 3 cm	222	25 (11.3)	15 (6.8)	60.0	9 (4.1)	36.0	1 (0.5)	4.0
1–2.9 cm	898	63 (7.0)	51 (5.7)	81.0	12 (1.3)	19.0	0 (0.0)	0.0
Benign (K-TRIADS 2)	53	0 (0.0)	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0

Numbers in parentheses are percentages. *Risk of each malignant tumor type in all nodules and at each nodule size category, †Proportion of each malignant tumor type among malignant tumors in all nodules and at each nodule size category, ‡p < 0.001 for trend toward decreasing risk of papillary carcinoma and increasing risk of follicular carcinoma and other malignant tumors with increasing nodule size. p < 0.001 for trend toward decreasing proportion of papillary carcinoma and increasing proportion of follicular carcinoma and other malignant tumors with increasing nodule size, §p = 0.004 for trend toward increasing overall malignancy risk as nodule size increases. p < 0.001 for trend of increasing risk of follicular thyroid cancer or other malignant tumors with increasing nodule size. p < 0.001 for trend toward decreasing proportion of papillary carcinoma and increasing proportion of follicular carcinoma and other malignant tumors with increasing nodule size, ‖p = 0.022 for trend toward increasing overall malignancy risk with increasing nodule size. p < 0.001 for trend of increasing risk of follicular thyroid cancer with increasing nodule size. p = 0.007 for trend toward decreasing proportion of papillary carcinoma. p = 0.016 for trend toward increasing proportion of follicular carcinoma with increasing nodule size.

respectively). The risk of PTC tended to be higher in nodules < 2 cm compared to nodules ≥ 2 cm (21.2% vs. 14.1%, respectively; $p = 0.051$). The risk of FTC and other malignant tumors was higher in nodules ≥ 2 cm compared to nodules < 2 cm ($p < 0.001$, respectively). Large nodules, ≥ 3 cm, showed a 4.2% decrease in the PTC risk, 22% increase in the non-PTC malignancy risk, and 17.7% increase in the overall malignancy risk compared with nodules < 3 cm.

In nodules with a low-suspicion US pattern, there was no significant difference in the risk of PTC and other malignant tumors according to nodule size ($p = 0.819$ and $p = 0.132$, respectively). However, there was a trend toward an increasing risk of FTC as the nodule size increased ($p = 0.001$), and the risk of FTC was higher in nodules ≥ 2 cm and nodules with a size of 2–2.9 cm compared to nodules < 2 cm ($p = 0.001$ and $p = 0.019$, respectively). Large nodules, ≥ 3 cm, showed a 1.1% increase in the PTC risk, 3.3% increase in the non-PTC malignancy risk, and 4.3% increase in the overall malignancy risk compared with nodules < 3 cm.

Distribution of Tumor Types according to Tumor Size and US Pattern in Malignant Tumors

Table 2 shows the distribution of malignant-tumor types according to tumor size and US pattern in malignant tumors. There was a trend toward a decreasing proportion of PTC and an increasing proportion of FTC and other malignant tumors among all malignant tumors as the tumor size increased ($p < 0.001$, respectively). The proportion of PTC was significantly higher in tumors < 2 cm compared to tumors ≥ 2 cm ($p < 0.001$). The proportion of FTC and other malignant tumors was significantly higher in tumors ≥ 2 cm compared to tumors < 2 cm ($p < 0.001$ and $p = 0.042$, respectively). There was no significant difference in the proportion of FTC and other malignant tumors between tumors with a size of 2–2.9 cm and tumors ≥ 3 cm ($p = 0.247$ and 0.091, respectively). The proportion of PTC among malignant tumors was higher in tumors with a high-suspicion US pattern than in tumors with intermediate- or low-suspicion patterns (94.8% vs. 75.6%, respectively; $p < 0.001$). However, the proportion of FTC was significantly higher in tumors with an intermediate- or low-suspicion US pattern than in tumors with a high-suspicion US pattern (19.1% vs. 2.1%, respectively; $p < 0.001$).

In nodules with a high-suspicion US pattern, there was a trend toward a decreasing proportion of PTC with increasing nodule size ($p = 0.025$). There was no significant difference in the proportion of FTC and other malignant tumors according to nodule size ($p \geq 0.078$). In nodules with an intermediate-suspicion US pattern, there was a trend toward a decreasing proportion of PTC and an increasing proportion of FTC and other malignant tumors ($p < 0.001$, respectively). The proportion of FTC and other malignant tumors was higher in nodules ≥ 2 cm compared to nodules < 2 cm ($p < 0.001$, respectively). In nodules with a low-suspicion US pattern, there was a trend toward a decreasing proportion of PTC ($p = 0.007$) and an increasing proportion of FTC ($p = 0.019$). There was no significant difference in the proportion of other malignant tumors according to nodule size ($p = 0.511$). There was a significant difference in the proportion of PTC and FTC between nodules ≥ 2 cm and nodules < 2 cm ($p = 0.005$ and 0.008, respectively).

DISCUSSION

Our study demonstrated that there was no increasing risk of malignancy as the nodule size increased. However, the impact of nodule size on the malignancy risk of nodules differed according to the US patterns of the nodules. There was no significant association between nodule size and the malignancy risk in nodules with a high-suspicion US pattern. Meanwhile, there was a trend toward an increased malignancy risk as the nodule size increased, and the malignancy risk of large nodules ≥ 3 cm was significantly higher than that of nodules < 3 cm in intermediate- or low-suspicion nodules. Regarding the risk and proportion of malignant-tumor types, there was a trend toward a decreasing risk and proportion of PTC and an increasing risk and proportion of FTC or other malignant tumors as the nodule size increased.

The differing impact of nodule size on the malignancy risk according to the US patterns of thyroid nodules may be explained by the difference in the impact of nodule size on the malignancy risk according to the histologic type of malignancy. Our results demonstrate different changes to the risk and proportion of malignant-tumor types between PTC and non-PTC malignant tumors as nodules increase in size. Therefore, the overall malignancy risk of nodules is determined by the balance of the malignancy risk between PTC and non-PTC malignant tumors at each nodule size. In high-suspicion nodules, most malignant tumors were PTC and there was no significant difference in the overall malignancy risk between large nodules ≥ 3 cm and nodules < 3 cm because the rates of a decreased risk of PTC and

Korean Journal of Radiology
KJR

increased risk of non-PTC malignancies were similar. In intermediate- or low-suspicion nodules, however, the proportion of non-PTC malignancy was approximately 5 times higher compared to that in high-suspicion nodules. The rate of increased risk of non-PTC malignancy was higher than that of the decreased risk of PTC in large intermediate-suspicion nodules ≥ 3 cm. There was no decreased risk of PTC, but there was an increased risk of FTC and other malignant tumors in large low-suspicion nodules ≥ 3 cm compared with smaller nodules < 3 cm. Therefore, the final calculated malignancy risk of intermediate- or low-suspicion nodules was significantly higher in large nodules, ≥ 3 cm, compared with smaller nodules.

Conflicting results have been reported regarding the association of nodule size and the malignancy risk of thyroid nodules. Several studies (6-8, 20, 21) reported that a large nodule size was associated with an increased malignancy risk. Kamran et al. (6) reported that increasing nodule size increased the cancer risk in a nonlinear fashion, and a size threshold of 2 cm was suggested. A recent systemic review (21) and meta-analysis (20) suggested that large nodules (> 3 cm or 4 cm) have a higher malignancy risk than smaller nodules. In contrast to that review, however, several studies (9-12) reported that larger nodules (> 3 cm or 4 cm) had a lower malignancy rate than smaller nodules. Cavallo et al. (9) reported that nodule size was inversely related to the malignancy risk, as larger nodules had lower malignancy, and nodules < 2 cm had the highest rate of malignancy. Other studies (8, 22-25) reported that there was no significant difference in the malignancy risk between large nodules (> 3 cm or 4 cm) and smaller nodules.

The prevalence of each histologic type of malignancy

Table 3. Comparison of Risk and Proportion of Histologic Type of Malignancy according to Nodule Size

Study	No. of Nodules	No. of Malignant Tumors (%)	Papillary Carcinoma		Follicular Carcinoma		Other Malignant Tumor		Follicular Carcinoma + Other Malignant Tumor	
			No. of Tumors (%)*	Proportion (%)†	No. of Tumors (%)*	Proportion (%)†	No. of Tumors (%)*	Proportion (%)†	No. of Tumors (%)*	Proportion (%)†
Kamran et al. (6)										
All	7348	927 (12.6)	808 (11.0)	87.2	78 (1.1)	8.4	40 (0.5)	4.3	118 (1.6)	12.7
≥ 3 cm	1771	279 (15.8)	220 (12.4)	78.9	38 (2.1)	13.6	20 (1.1)	7.2	58 (3.3)	20.8
1–2.9 cm	5577	648 (11.6)	588 (10.5)	90.7	40 (0.7)	6.2	20 (0.4)	3.1	60 (1.1)	9.3
≥ 2 cm	3727	544 (14.6)	455 (12.2)	83.6	56 (1.5)	10.3	32 (0.9)	5.9	88 (2.4)	16.2
1–1.9 cm	3621	383 (10.6)	353 (9.7)	92.2	22 (0.6)	5.7	8 (0.2)	2.1	30 (0.8)	7.8
Deveci et al. (26)										
All	559	234 (41.9)	190 (34.0)	81.2	39 (7.0)	16.7	5 (0.9)	2.1	44 (7.9)	18.8
> 3 cm	132	57 (43.2)	41 (31.1)	71.9	14 (10.6)	24.6	2 (1.5)	3.5	16 (12.1)	28.1
1.1–3 cm	427	177 (41.5)	149 (34.9)	84.2	25 (5.9)	14.1	3 (0.7)	1.7	28 (6.6)	15.8
> 2 cm	290	122 (42.1)	95 (32.8)	77.9	23 (7.9)	18.9	4 (1.4)	3.3	27 (9.3)	22.1
1.1–2 cm	269	112 (41.6)	95 (35.3)	84.8	16 (5.9)	14.3	1 (0.4)	0.9	17 (6.3)	15.2
Cavallo et al. (9)										
All	868	215 (24.8)	190 (21.9)	88.4	15 (1.7)	7.0	10 (1.2)	4.7	25 (2.9)	11.6
≥ 3 cm	296	58 (19.6)	45 (15.2)	77.6	8 (2.7)	13.8	5 (1.7)	8.6	13 (4.4)	22.4
1–2.9 cm	572	157 (27.4)	145 (25.3)	92.4	7 (1.2)	4.5	5 (0.9)	3.2	12 (2.1)	7.6
≥ 2 cm	517	105 (20.3)	85 (16.4)	81.0	14 (2.7)	13.3	6 (1.2)	5.7	20 (3.9)	19.0
1–1.9 cm	351	110 (31.3)	105 (29.9)	95.5	1 (0.3)	0.9	4 (1.1)	3.6	5 (1.4)	4.5
Current study										
All	2000	454 (22.7)	388 (19.4)	85.5	48 (2.4)	10.6	18 (0.9)	4.0	66 (3.3)	14.5
≥ 3 cm	329	71 (21.6)	40 (12.2)	56.3	21 (6.4)	29.6	10 (3.0)	14.1	31 (9.4)	43.7
1–2.9 cm	1671	383 (22.9)	348 (20.8)	90.9	27 (1.6)	7.0	8 (0.5)	2.1	35 (2.1)	9.1
≥ 2 cm	715	142 (19.9)	92 (12.9)	64.8	36 (5.0)	25.4	14 (2.0)	9.9	50 (7.0)	35.2
1–1.9 cm	1285	312 (24.3)	296 (23.0)	94.9	12 (0.9)	3.8	4 (0.3)	1.3	16 (1.2)	5.1

Numbers in parentheses are percentages. *Risk of each malignant tumor type in all nodules and at each nodule size category, †Proportion of each malignant tumor type among malignant tumors in all nodules and at each nodule size category.

was analyzed according to nodule size in three relevant studies (6, 9, 26), which reported different results. Table 3 shows the comparative data of the risk and proportion of malignant-tumor types according to nodule size in these three studies (6, 9, 26) and the current study. All three studies and our study consistently demonstrated that non-PTC malignancy had a higher risk and proportion of malignant tumors in large nodules at each size threshold of 2 cm or 3 cm. The rate of increased risk of non-PTC malignancy in a large nodule size was similar in two studies reporting different results (6, 9). Although all studies showed a lower proportion of PTC among malignancy in large tumors, the relationship between the risk of PTC and nodule size differed according to the studies. Kamran et al. (6) reported a higher risk of PTC in large nodules at each size threshold of 2 cm or 3 cm. In contrast to that, Cavallo et al. (9) reported a lower risk of PTC in large nodules at each size threshold. The proportion of non-PTC malignant tumors among malignancies may be an important factor that influences the overall malignancy risk according to nodule size because the previous studies and our study consistently showed a close relationship between the increasing risk of non-PTC malignant tumors and the increasing nodule size. However, the proportions of PTC among all malignant tumors in each study population were similar across the studies; 78.1–91.6% in studies that reported a higher malignancy risk in large nodules (6-8), and 88.4–90.9% in studies that reported a lower malignancy risk in large nodules (9-11). Meanwhile, the distribution of PTC according to tumor size differed among the studies. The proportion of PTC with a size < 2 cm was 43.7% in the study by Kamran et al. (6), 55.3% in the study by Cavallo et al. (9), and 76.3% in the current study. Therefore, the difference in the risk of PTC according to nodule size may result mainly from the difference in the size distribution of PTC, and the malignancy risk of nodules according to nodule size could be different depending on the size distribution of PTC even in the study populations with the same overall malignancy rate and proportion of malignant-tumor types. The higher proportion of relatively small PTC < 2 cm indicates the higher proportion of early detected PTC, which may be closely related to the high utilization of US diagnosis in a high-resource society (27) and the application of sensitive FNA criteria for the detection of malignancy.

Several factors for potential bias should also be considered in the assessment of the malignancy risk according to nodule size. First, many previous studies (8-12) used surgical diagnosis as the final diagnosis of thyroid nodules, which might have overestimated the malignancy risk of small nodules because the majority of small nodules with benign FNA results do not require surgery. Second, the larger FNA size cutoff for nodules with low- or intermediate-suspicion US patterns may inevitably result in delayed diagnosis of malignancy and a higher frequency of malignancies with low- or intermediate-suspicion US patterns in large nodules. In our study, the effect of these factors could be minimized because a benign FNA result as well as surgical diagnosis was used for the reference standard of a benign nodule, and FNA was performed in most intermediate- or low-suspicion nodules, ≥ 1 cm, during the study period. Our results may raise a presumption that the false negative rate of benign FNA cytology result might be higher in large (≥ 3 cm) intermediate- or low-suspicion nodules than in small intermediate- or low- suspicion nodules because the malignancy risk of large (≥ 3 cm) nodules was higher compared with relatively small nodules and the proportion of FTC that induces higher false-negative rates of FNA (28) was higher in large intermediate- or low-suspicion nodules. However, it requires further investigation to determine whether the false-negative rate of benign FNA cytology result may increase in large intermediate- or low-suspicion nodules.

There are several limitations to this study. First, selection bias may have existed because some patients without a final diagnosis were excluded. Second, the proportion of relatively small PTC (< 2 cm) was higher in our study population, and our study results should be verified in a study population with a different size distribution of PTC.

In conclusion, the impact of nodule size on the malignancy risk differed according to the histologic type of malignant tumors and the US pattern. Although a large nodule size did not increase the malignancy risk in high-suspicion nodules, a large nodule size did increase the malignancy risk in low- or intermediate-suspicion nodules. Therefore, nodule size should be considered for the estimation of the malignancy risk in intermediate- or low-suspicion nodules.

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