



Extrathyroidal Extension in Papillary Thyroid Cancer Could be Predicted Through Preoperative Sonography

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Background and Objectives: Surgical decision-making for papillary thyroid cancer (PTC) relies on accurate preoperative staging, where ultrasonography plays a crucial role in predicting outcomes. We aimed to analyze the predictive effects of preoperative sonographic findings on pathological characteristics. **Materials and Methods:** Retrospective study was performed using ultrasonographic images and clinico-pathologic data of papillary thyroid cancer patients who underwent total thyroidectomy or lobectomy between March 2016 and May 2020. Finally, 152 patients and 169 tumors were analyzed. **Results:** Mean age of patients was 54.2±14.2 years and the proportion of female was 75.7%. Tumor size was 13.6±10.3 mm and the proportions of extrathyroidal extension (ETE) and lymph node (LN) involvement were 52.2% and 23.0%, respectively. Preoperative sonographic findings, including ETE, tumor margin, echogenicity, and K-TIRADS, were significantly associated with pathological ETE. Other pathological characteristics, including LN involvement, lymphovascular invasion, and resection margin positivity, were more observed in patients with more aggressive findings on preoperative sonography; however, we could not find statistical significances. **Conclusion:** This study showed that preoperative sonographic characteristics, such as sonographic ETE, tumor margin, echogenicity, and K-TIRADS, can provide valuable insights into predicting pathological ETE in PTC patients.

Key Words: Papillary thyroid cancer, Ultrasonography, Extrathyroidal extension, Lymph node involvement, K-TIRADS

Introduction

Ultrasonography (US) has been the modality of choice for the preoperative evaluation of papillary thyroid carcinoma (PTC).¹⁻³ Because tumor size, age, extrathyroidal extension (ETE), lymph node (LN) metastasis, and tumor multiplicity are known risk factors for the recurrence of PTC,⁴⁻⁷ the extent of surgery was determined based on the preoperative staging of PTC,

and preoperative staging US is essential for surgical planning and predicting patient outcomes.⁸⁻¹⁰

Several studies had reported the clinical usefulness of preoperative sonography.¹¹⁻¹⁴ While sonography has demonstrated good performance in predicting ETE or cervical LN metastasis, we wondered whether the subtype of each sonographic finding might indicate varying risks of aggressiveness in the surgical specimen.

We analyzed the predictive usefulness of preoperative sonographic findings to expect pathological

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characteristics, using data from patients with papillary thyroid cancer. In our study, our study indicates that pathologically diagnosed ETE could be anticipated through various preoperative sonographic characteristics, including sonographic ETE, resection margin, echogenicity, and Korean Thyroid Imaging Reporting and Data System (K-TIRADS).

Materials and Methods

Subjects

We retrospectively analyzed the data of patients who underwent total thyroidectomy or lobectomy at Kangwon National University Hospital between March 2016 and May 2020. Among a total of 217 cases, 34 benign results such as nodular hyperplasia, follicular adenoma, and adenomatous goiter were excluded, and non-invasive follicular thyroid neoplasms with papillary-like nuclear features were excluded for borderline malignancy. We also excluded other malignancies, such as two Hurtle cell carcinomas, two follicular carcinomas, and one each of poorly-differentiated carcinoma, adenoid cystic carcinoma, and metastasis. Four complete thyroidectomy cases were also excluded. Finally, 159 patients (169 nodules), including 37 men and 122 women, were included in this study. This retrospective study was conducted with the institutional review board's approval (KNUH-2021-07-027), and the requirement for patients' informed consent was waived.

US Examination and Image Review

Thyroid US was performed by radiologists using high-resolution US equipment with a 5–12 MHz linear array transducer (IU 22; Philips Healthcare, Bothell, WA, USA). Two experienced radiologists (with 10 and 7 years of clinical experience in thyroid imaging) were retrospectively reviewed. Each radiologist independently reviewed the images, while blinded to the clinical and histopathological data. Tumor size, location, echogenicity, margin, orientation, parenchymal echogenic foci (microcalcifications), ETE, and K-TIRADS were analyzed using the preoperative US. According

to the previous study,¹⁵⁾ ETE was categorized into four groups: 'absent', 'abutment', 'capsular disruption', and 'protrusion'. The 'protrusion' category included 'contour bulging' and 'replacement of strap muscle'. The K-TIRADS classification of nodules was applied according to the updated 2021 guideline.¹⁶⁾

Table 1. Clinicopathological characteristics for patients (n=152) and nodules (n=161)

Variables	Values
Age	53.6 ± 14.3
Male/female	37/115 (24.3%/75.7%)
Sonographic findings	
Tumor size (mm)	14.9 ± 10.3
Location	
Upper	59 (36.6%)
Middle	54 (33.5%)
Lower	48 (29.8%)
Echogenicity	
Isoechogenicity	15 (9.3%)
Mild hypoechogenicity	57 (35.4%)
Marked hypoechogenicity	89 (55.3%)
Margin	
Smooth	33 (20.5%)
Ill-defined	47 (29.2%)
Irregular	81 (50.3%)
Orientation	
Parallel	73 (45.6%)
Nonparallel	87 (54.4%)
Parenchymal echogenic foci	82 (51.2%)
Extrathyroidal extension	
Absent	48 (30.0%)
Abutment	66 (41.2%)
Capsular disruption	29 (18.1%)
Protrusion	17 (10.6%)
K-TIRADS	
Category 3	8 (5.0%)
Category 4	38 (23.6%)
Category 5	115 (71.4%)
Pathologic findings	
Tumor size (mm)	13.6 ± 10.3
Multiplicity	59 (36.6%)
Extrathyroidal extension	
Absent	77 (47.8%)
Microscopic	80 (49.7%)
Gross	4 (2.5%)
Lymphovascular invasion	17 (10.6%)
Resection margin involvement	21 (13.0%)
Lymph node involvement	37 (23.0%)

K-TIRADS: Korean Thyroid Imaging Reporting and Data System

Statistical Analysis

The proportion of each pathologic characteristic (tumor size, ETE, lymphovascular invasion, resection margin involvement, and LN involvement) was compared according to sonographic characteristics (size, echogenicity, margin irregularity, orientation, presence of echogenic foci, presence of ETE, and K-TIRADS) using the chi-square test. The trend of this proportion was evaluated using the Cochran-Armitage test. Logistic regression analysis was performed to analyze the risk effect of each preoperative sonographic characteristic for pathologic features. Statistical analyses were performed using the STATA 16 (College Station, TX, StataCorp LLC, College Station, TX, USA), and p-values <0.05 were considered statistically significant.

Results

Clinicopathological Characteristics

Of a total of 159 patients (169 nodules), the mean age was 54.2 ± 14.2 years (ranged 26 to 88 years), and there were 37 (23.2%) males and 122 (76.8%) females. Table 1 shows that the average tumor size was 14.9 ± 10.3 mm, the proportions of tumor location were 36.6% in upper, 33.5% in middle, and 29.8% in lower. About preoperative sonographic characteristics, mild or marked hypoechogenicity was observed in 90.7%, irregular margin in 50.3%, and nonparallel orientation in 54.4%. Abutment with thyroid capsule was observed in 66 nodules (41.2%), capsular disruption in 29 nodules (18.1%), and protrusion in 17 (10.6%). Of the 17 cases with protrusion, 10 cases (58.8%) exhibited 'contour bulging', while 7 cases (41.2%) showed 'replacement of strap muscle'. There were no nodules with 'obtuse angle to the trachea' or 'postero-

Table 2. The proportion of pathological characteristic according to preoperative sonographic characteristics

Sonographic features	Pathologic features							
	ETE		LN involvement		Lymphovascular invasion		RM positivity	
	Case (%)	p (p for trend)	Case (%)	p (p for trend)	Case (%)	p (p for trend)	Case (%)	p (p for trend)
ETE on sonography		<0.001		0.195		0.045		0.172
None	12 (25.0%)	(<0.001)	8 (16.7%)	(0.037)	1 (2.1%)	(0.515)	4 (8.3%)	(0.047)
Abutment	40 (60.6%)		14 (21.2%)		12 (18.2%)		8 (12.1%)	
Capsular disruption	18 (62.1%)		8 (27.6%)		3 (10.3%)		4 (13.8%)	
Protrusion	13 (76.5%)		7 (41.2%)		1 (5.9%)		5 (29.4%)	
Margin		<0.001		0.164		0.428		0.157
Smooth	8 (24.2%)	(<0.001)	4 (12.1%)	(0.058)	2 (6.1%)	(0.200)	1 (3.0%)	(0.088)
Ill-defined	21 (44.7%)		10 (21.3%)		4 (8.5%)		7 (14.9%)	
Irregular	55 (67.9%)		23 (28.4%)		11 (13.6%)		13 (16.1%)	
Echogenicity		0.002		0.135		0.868		0.118
Isoechoic	2 (13.3%)	(<0.001)	1 (6.7%)	(0.047)	1 (6.7%)	(0.645)	1 (6.7%)	(0.058)
Mild hypoechoic	27 (47.4%)		11 (19.3%)		6 (10.5%)		4 (7.0%)	
Marked hypoechoic	55 (61.8%)		25 (28.1%)		10 (11.2%)		16 (18.0%)	
K-TIRADS		<0.001		0.267		0.603		0.484
3	0 (0)	(<0.001)	0 (0)	(0.427)	0 (0)	(0.442)	0 (0)	(0.667)
4	14 (36.8%)		10 (26.3%)		4 (10.5%)		6 (15.8%)	
5	70 (60.9%)		27 (23.5%)		13 (11.3%)		15 (13.0%)	

ETE: extrathyroidal extension, K-TIRADS: Korean Thyroid Imaging Reporting and Data System, LN: lymph node, RM: resection margin

medial protrusion to tracheoesophageal groove'. According to K-TIRADS, 115 nodules (71.4%) were defined as category 5, 38 nodules (23.6%) as category 4, and 8 nodules (5.0%) as category 3. In pathologic characteristics, the tumor size was 13.6 ± 10.3 mm, and multiplicity was observed in 59 (36.6%). Microscopic ETE was observed in 49.7%, gross ETE was noted in 2.5%. Lymphovascular invasion was noted in 10.6%, and resection margin invasion was noted in 13.0%. LN involvement was observed in 23.0%.

Proportion of Each Pathological Characteristics According to Sonographic Features

In surgical pathology, ETE was more frequently observed in the nodules with more aggressive sonographic characteristics, such as abutment to protrusion in ETE, irregular tumor margin, isoechoic to marked hypoechoic in echogenicity, and 3 to 5 in K-TIRADS (Table 2).

For the LN involvement, ETE and echogenicity in preoperative sonographic characteristics showed significant increasing trend of the proportion of LN involvement. Resection margin (RM) positivity was also more frequently observed in nodules with ETE in preoperative sonography. Lymphovascular invasion in surgical pathology did not show different frequencies among the preoperative sonographic characteristics.

Risk of Preoperative Sonographic Characteristics for Each Pathologic Characteristic

Fig. 1 shows the risk effects of each sonographic findings to expect pathologic characteristics in surgical pathology. For the ETE in surgical pathology, all ETE findings of preoperative sonography showed significant risk effect, and protrusion had highest odds ratio. Irregular margin also showed significant risk for ETE, and both of mild and marked hypoechoic showed significant risk. TIRADS also was significant risk feature for ETE in surgical specimen. For the other pathological characteristics, sonographic characteristics showed overall increasing risk; however statistical significances were observed only in protrusion for LN involvement and RM positivity and in lymphovascular invasion for abutment.

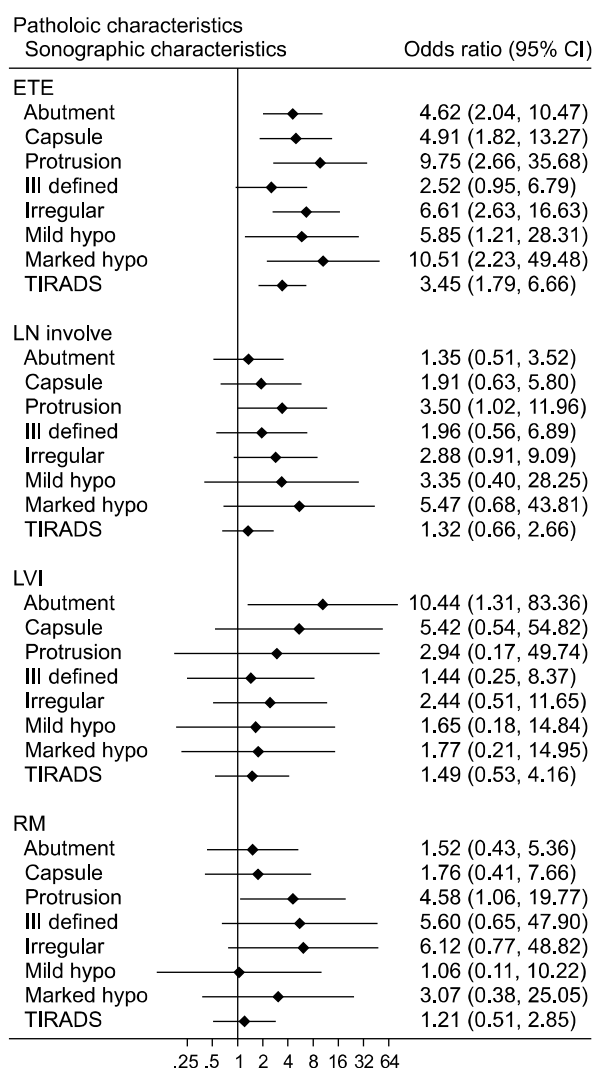


Fig. 1. Risk effect of each preoperative sonographic characteristics for pathologic characteristics. The diamond point on the graph indicates the odds ratios, and the horizontal bar indicates the its 95% confidence intervals. ETE: extrathyroidal extension, K-TIRADS: Korean Thyroid Imaging Reporting and Data System, LN: lymph-node, LVI: lymphovascular invasion, Spi/lobul: spiculated/lobulated, RM: resection margin

Discussion

Revised eighth TNM staging system, tumor size, extrathyroidal extension, and nodal metastasis are important factors in the prognosis of papillary thyroid carcinoma,¹⁷⁾ close and careful review of the tumor size, ETE, and suspicious LN is required on preoperative US examination. In this study, we evaluated the association between various findings on the pre-

operative US and pathologic reports. In univariate analyses, ETE on the US, echogenicity of nodules, irregular margin, and K-TIRADS categorization were related to pathologic ETE. Additionally, protruding nodules showed positive relationships with pathologic ETE, LN metastasis, and resection margin positivity. This is consistent with multiple previous studies and the prior literature.^{1,8-10,15,18)} Among the pathological characteristics associated with patients' outcomes, ETE finding was predictable from various sonographic characteristics, including K-TIRADS. On the contrary, other pathological characteristics (LN involvement, lymphovascular invasion, and RM positivity) were hard to be discriminated by preoperative sonographic characteristics. These results also were observed in multivariate analysis with adjustment for age and sex. The risk of ETE was significantly elevated in nodules with any aggressive characteristics on preoperative sonography. Given that extension to extrathyroidal tissues could affect surgical extension and patients' outcome and that we can discriminate ETE using sonographic examination, meticulous examination could be important in preoperative period.

Unfortunately, the other pathological characteristics, including LN involvement, lymphovascular invasion, and RM positivity, did not show significant association with sonographic characteristics. In papillary thyroid cancer, lymph node involvement or lymphovascular invasion is usually observed in microscopic examinations, making it challenging to detect these features grossly in sonographic examinations. Given that RM positivity also be diagnosed in pathologic specimens after surgical resection, sonography could not discriminate RM positivity. Nevertheless, considering that these sonographic findings showed overall positive risk with pathological characteristics, further studies with more meticulous sonographic examination about these characteristics and larger sample size might observe the statistical significances.

Our study had several limitation as a retrospective observational study. Firstly, this study included only patients who were diagnosed as papillary thyroid cancer and underwent thyroidectomy, resulting in selection bias that patients with more aggressive

characteristics. To assess the risk of malignancy based on sonographic findings, it was necessary to compare the differences between malignant nodules and benign nodules. Secondly, our sample size might be insufficient to detect statistically significant differences in the association between sonographic and pathological characteristics.

In conclusion, our study showed that pathological ETE could be expected by preoperative sonographic characteristics, including sonographic ETE, resection margin, echogenicity, and K-TIRADS.

Author Contributions

Conceptualization: Hoonsung Choi, Go Eun Yang. Date acquisition: Hwan Soo Kim, Yoon Jong Ryu, Kyoung Yul Lee. Investigation: Go Eun Yang, Taek Geun Ohk. Methodology: Hoonsung Choi. Supervision: Sung Whi Cho. Writing: Go Eun Yang.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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