High suspicion US pattern on the ATA guidelines, not cytologic diagnosis, may be a predicting marker of lymph node metastasis in patients with classical papillary thyroid carcinoma

Eun Cho, MD [a, b], Eun-Kyung Kim, MD [a], Hee Jung Moon, MD [a], Jung Hyun Yoon, MD [a], Vivian Y. Park, MD [a], Jin Young Kwak, MD [a, *]

[a] Department of Radiology, Severance Hospital, Research Institute of Radiological Science, Yonsei University, College of Medicine, Seoul, South Korea
[b] Department of Radiology, Dong-A University Hospital, Dong-A University, College of Medicine, Busan, South Korea

ARTICLE INFO

ABSTRACT

Background: To evaluate the utility of ultrasound (US) patterns based on the 2015 American Thyroid Association (ATA) guidelines and cytologic diagnosis of the Bethesda System for Reporting Thyroid Cytopathology as predicting markers for lymph node metastasis (LNM) in classical papillary thyroid carcinoma (PTC).
Methods: A retrospective analysis of 657 patients with classical PTC who underwent ultrasound-guided fine-needle aspiration (US-FNA) and surgery were included in this study. The associations between LNM and the US features or the Bethesda System for Reporting Thyroid Cytopathology were evaluated.
Results: Multivariate logistic regression analysis showed that the high suspicion US pattern was independently associated with LNM (odds ratio = 3.081; 95% confidence interval = 1.515–6.262; $P = .002$). And the Bethesda category was not significantly associated with LNM ($P = .056$).
Conclusions: The high suspicion US pattern of the 2015 ATA guidelines, not cytologic diagnosis, could be a predicting marker of LNM in patients with classical PTC.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common subset of thyroid cancer, and patients with PTC generally have good prognosis. Nevertheless, about 9–26% of these patients suffer from recurrence, and the multiple independent risk factors of recurrence in PTC have been reported.[1–7] Among them, lymph node metastasis (LNM) in patients with PTC is one well-known and strong predictor of recurrence.[3,6,7]

For risk stratification for patients with PTC, several molecular markers have been investigated, including mutations on the B-type Raf (BRAF) proto-oncogene or serine/threonine kinase and telomerase reverse transcriptase (TERT) promoter mutation, which suggest poor patient outcomes.[8–11] The TERT promoter mutations is associated with the aggressive thyroid carcinomas, such as BRAF

mutation-positive PTC.[12] Especially, the coexistence of BRAF[V600E] mutation and TERT[c.228C>T] mutation could increase the risk of the recurrence.[11] However, these molecular analyses require high cost and long process time.

Ultrasonography (US) and cytologic features have been reported as to be associated with the patient prognosis in PTC.[13–16] Malignant-appearing PTCs showing at least 1 suspicious sonographic feature - taller than wide shape, marked hypoechogenicity, microcalcifications, and infiltrative border -were reported to be associated with LNM and higher rate of recurrence.[15,16] And the number of suspicious US features classified by the Thyroid Imaging Reporting and Data System (TI-RADS) was also associated with lateral LNM.[17] However, the association between the cytologic features and LNM is still debatable.[13,14,18]

Recently, according to the revised 2015 ATA management guidelines, thyroid nodules can be classified into the following five categories according to US pattern and risk of malignancy: (a) high suspicion, (b) intermediate suspicion, (c) low suspicion, (d) very low suspicion, and (e) benign.[19] (Table 1) However, to our knowledge, there has been no published study evaluating the association

* Corresponding author. Department of Radiology, Severance Hospital, Research Institute of Radiological Science, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, 03722, Seoul, South Korea.
E-mail address: docjin@yuhs.ac (J.Y. Kwak).

Table 1
Ultrasonographic patterns and estimated risk of malignancy for thyroid nodules according to the revised 2015 ATA management guidelines.

Ultrasonographic pattern	US features	Estimated risk of malignancy (%)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	>70–90
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension, or taller than wide shape	10–20
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape.	5–10
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	<3
Benign	Purely cystic nodules (no solid component)	<1

between US patterns of the ATA guidelines of classical PTC and poor prognostic factors such as LNM. Therefore, we investigated the utility of US patterns based on the 2015 ATA guidelines and cytologic diagnosis of the Bethesda System for Reporting Thyroid Cytopathology as a predicting marker for LNM in classical PTC.

2. Materials and methods

This study was of a retrospective design and was approved by our institutional review board. Informed consent was waived for this study, but was obtained for US-guided fine needle aspiration (US-FNA) and surgery from all patients before each procedure.

2.1. Patients

From March 2013 to February 2014, 3107 patients underwent US-FNA for diagnosis at our institution. Among the 3107 patients, 894 consecutive patients underwent thyroidectomy at our institution. Of these patients, 795 patients were confirmed with thyroid cancer on surgery, and 735 patients had PTC. Patients diagnosed with PTC of other variants were excluded from this study. In total, 657 patients with classical PTC diagnosed by surgical pathology were included. The mean and standard deviation of patient age at diagnosis was 47.2 ± 13.0 years (range, 13–86 years; 513 women [mean age, 46.7 ± 13.1 years; range, 13–86 years] and 144 men [mean age, 49.3 ± 12.8 years; range, 27–81 years]). The mean tumor size was 9.1 ± 6.2 mm (range, 1–51 mm) (see Table 2).

2.2. US examinations

Preoperative thyroid US were performed by one of ten board-certified radiologists (4 faculties and 6 fellows) with 1–19 years of experience who were specialized in thyroid imaging, using a 5–12 MHz linear array transducer (iU22; Philips Medical Systems, Bothell, Wash, USA). US-FNAs were then performed by the same radiologist who fulfilled the thyroid US.

The radiologist who performed the US examination recorded prospectively the US features of the thyroid nodules in our institutional database according to the following criteria: composition (solid, predominantly solid with a solid portion of over 50% in a mixed nodule, predominantly cystic with a solid portion of less than 50% in a mixed nodule, or spongiform), echogenicity (hyper-, iso-, or hypoechogenicity compared with the echogenicity of the surrounding normal thyroid parenchyma, or marked hypoechogenicity compared with the echogenicity of the adjacent strap muscle), margin (well-circumscribed, microlobulated, or irregular margins), calcification (microcalcifications, mixed calcifications, macrocalcifications, eggshell calcifications, or no calcification), and

shape (parallel or non-parallel, greater in the anteroposterior dimension than in the transverse dimension).[20] The US features considered suspicious for malignancy were solid composition, hypoechogenicity or marked hypoechogenicity, microlobulated or irregular margins, presence of microcalcifications, and non-parallel shape, based on published criteria.[20–23] The US patterns prospectively described were categorized retrospectively based on the 2015 ATA management guidelines by one radiologist (K.J.Y., 16 years of experience in thyroid imaging).[19]

2.3. US-FNA procedures and cytopathologic analyses

US-FNA was performed in nodules with at least one of the above-mentioned suspicious US features or in the largest nodule when none of the multiple nodules detected on US had suspicious findings. A 23-gauge needle attached to a 2-mL disposable syringe was used for US-FNA with the free-hand technique. Each lesion was aspirated and the obtained material was expelled and underwent alcohol-fixed smearing on glass slides with 95% ethanol for

Table 2
Patient demographics and clinical characteristics.

Variables	Total (N = 657)
Age at diagnosis (year)	47.2 ± 13.0
Gender	
Male	144 (21.9)
Female	513 (78.1)
2015 ATA US pattern	
High suspicion	593 (90.3)
Intermediate suspicion	45 (6.8)
Low suspicion	16 (2.4)
Very low suspicion	3 (0.5)
Bethesda category	
III	39 (5.9)
V	151 (23.0)
VI	467 (71.1)
Tumor size (mm)	9.1 ± 6.2
Lymph node metastasis	
Negative	425 (64.7)
Central	224 (34.1)
Lateral	54 (8.2)
AJCC stage	
Advanced (Stage III-IV)	9 (1.4)
Limited (Stage I-II)	648 (98.6)

Note. - Numeric data are presented as mean ± SD (standard deviation). Non-numeric data are presented as number of patients (percentage).
- Categories of the Bethesda System for Reporting Thyroid Cytopathology described in the table are as follows:
- Category III: atypia of undetermined significance or alternatively follicular lesion of undetermined significance.
- Category V: suspicious for malignancy.
- Category VI: malignant.