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● *Original Contribution*

ASSOCIATION BETWEEN BETHESDA CATEGORIES AND ULTRASOUND FEATURES OF CONVENTIONAL PAPILLARY THYROID CARCINOMA

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Abstract—The association between categories 3, 5 and 6 of the Bethesda System for Reporting Thyroid Cytopathology and the clinical and ultrasonography (US) features of conventional papillary thyroid carcinoma (PTC) was evaluated. We included 2005 patients diagnosed with conventional PTC at surgery and Bethesda categories 3, 5 and 6 at pre-operative US-guided fine-needle aspiration. Multinomial regression analysis was performed to determine the odds ratio (ORs) of each US feature associated with category 3 or 5, with category 6 as reference. Category 3 and 5 PTCs were smaller (ORs = 0.925 and 0.937) and did not exhibit marked hypo-echogenicity (ORs = 0.341 and 0.268) compared with category 6 PTCs. Category 3 and 5 PTCs exhibited significant macrocalcification (ORs = 2.372 and 1.594) and heterogeneous parenchyma (OR = 1.265 in category 5). In conclusion, conventional PTCs pre-operatively aspirated as Bethesda category 3, 5 or 6 significantly differ in size, macrocalcification, underlying thyroid parenchymal echogenicity and final assessment of US features. (E-mail: artemis4u@yuhs.ac) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Papillary thyroid carcinoma, Conventional subtype, Ultrasonography, Fine-needle aspiration, Bethesda category.**

INTRODUCTION

Conventional papillary thyroid carcinoma (PTC) is the most common thyroid cancer. Its nuclear features, such as nuclear pseudo-inclusions, nuclear grooves, ground glass nuclei, overlapping and crowded nuclei, ovoid nuclei and enlarged and irregularly shaped nuclei, are the gold standard for diagnosing PTC (Kwak et al. 2009; Verhulst et al. 2008). The Bethesda System for Reporting Thyroid Cytopathology introduced a six-category standardization to promote uniform practice and communication in the management of thyroid nodules (Cibas et al. 2009). Unlike Bethesda category 6 for PTC, Bethesda category 5, suspicious for malignancy, is assigned when a cytomorphologic diagnosis of PTC cannot be made with certainty (Cibas et al. 2009). Assignment of PTCs to Bethesda category 3, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), remains controversial, with

variable incidence rates and risks of malignancy being reported (Cibas et al. 2009). The recommended risks of malignancy associated with Bethesda categories 6, 5 and 3 are 97%–99%, 60%–75%, and 5%–15%, respectively (Cibas et al. 2009).

Kleiman et al. (2013) and VanderLaan et al. (2012) discussed the relationship between conventional PTCs and different Bethesda categories. To our knowledge, however, there have been no published reports focusing on the ultrasonography (US) features of only conventional PTCs associated with Bethesda categories 3, 5 and 6 using large-sample data. Therefore, we evaluated the association between Bethesda categories 3, 5 and 6 and US features in surgically confirmed conventional PTCs.

METHODS

Study sample and data collection

Institutional review board approval was obtained and informed consent was waived for this retrospective study. Written informed consent was obtained from all patients for US-guided fine-needle aspiration (US-FNA) before each procedure as part of daily clinical practice.

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From August 2012 to July 2013, a total of 2254 consecutive patients underwent pre-operative US and thyroid surgery in our institution. All patients underwent pre-operative US-FNA either in our institution (n = 439) or in outside clinics (n = 1815). US-FNAs performed in outside clinics were reviewed by the pathology department of our institution with FNA slides. Among 2254 patients, 2066 were diagnosed with conventional PTC on surgery. One of the 2066 patients was excluded as the patient had PTC exhibiting microcalcification only. Among the 2065 patients, 2005 were reported to have Bethesda category 3, 5 or 6 on pre-operative US-FNA: category 3 (111 cases, 5.5%), category 5 (657 cases, 32.8%), category 6 (1237 cases, 61.7%) (Table 1). Finally, a total of 2005 patients were included in our study (Fig. 1).

The mean age of the 2005 patients was 44.0 ± 11.7 y (range, 12–85 y). Four hundred fourteen patients were male, and 1591 were female. The mean US-measured size of the 2005 index PTCs that had undergone US-FNA was 9.8 ± 6.8 mm (range, 2–92 mm). Of the 2005 index PTCs, 1382 were ≤10 mm and 623 were >10 mm on US.

US examinations, US-FNA and cytologic analyses

Pre-operative US has been routinely performed on patients for whom thyroid surgery is planned at our institution since 2006. A 5- to 12-MHz linear probe (iU22, Philips Medical Systems, Bothell, WA, USA) or a 6- to 13-MHz linear probe (EUB-7500, Hitachi Medical, Tokyo, Japan) was used for thyroid gland and lymph node evaluation. Thirteen board-certified radiologists specializing in thyroid imaging, with 1–16 y of experience, performed pre-operative US examinations during the study period. Their findings were prospectively reported in radiologic reports. The index tumor size on US was measured at the maximum dimension. US features were classified by composition (solid, solid portion <50% or solid portion >50%); echogenicity (hyper-, iso- or, hypo-echogenicity compared with the surrounding thyroid gland, or marked hypo-echogenicity compared with the strap muscle); margin (well-defined, microlobulated or irregular); calcification

(microcalcification [hyper-echoic foci <1 mm with or without acoustic shadows], macrocalcification or no calcification); shape (wider than tall or taller than wide); vascularity (central, peripheral or no vascularity); and underlying parenchymal echogenicity (homogeneous or heterogeneous). Mixed calcification was defined as a combination of microcalcification and macrocalcification and was considered microcalcification. Marked hypo-echogenicity, irregular or microlobulated margin, presence of microcalcification and taller than wide shape were regarded as suspicious US features (Kim et al. 2002; Moon et al. 2010; 2012). Radiologists chose one of two categories (homogeneous or heterogeneous) with respect to the underlying parenchymal echogenicity because diffuse heterogeneous parenchymal echogenicity and coarse echotexture had been considered as findings of underlying diffuse thyroid disease (Kim et al. 2010; 2014; Pedersen et al. 2000). Thyroid nodules with one or more of the mentioned suspicious US features were assessed as "suspicious," and nodules without suspicious US features were assessed as "probably benign."

The Bethesda classification has been used since December 2009 at our institution. Bethesda category 6 is assigned whenever cytomorphologic features are conclusive for PTC (Cibas and Ali 2009; Cibas et al. 2009). If only one or two characteristic features of PTC are present, and if they are only focal and not widespread throughout the follicular cell population, or if the sample is sparsely cellular, a malignant diagnosis cannot be made with certainty and the nodules are classified as Bethesda category 5 (Cibas and Ali 2009; Cibas et al. 2009). Bethesda category 3 is assigned when thyroid FNAs are not easily classified into the benign, suspicious or malignant category (Cibas and Ali 2009; Cibas et al. 2009). During the study period, cytologic diagnosis was performed by one of five pathologists with at least 3 y of experience in thyroid cytopathology, and the performing pathologist was arbitrarily assigned according to the hospital schedule.

Statistical analysis

Clinical features including US features of the three groups and Bethesda category 3, 5 or 6 were compared using the χ^2-test or Fisher's exact test for categorical variables and analysis of variance or the Kruskal–Wallis test for continuous variables. *Post hoc* pairwise analysis was performed with a Bonferroni correction, where a p value of 0.0167 (0.05/3) was considered to indicate a significant difference. Multinomial logistic regression analysis was used to assess independent associations between Bethesda categories and US features that had a p value < 0.1 in univariate analysis, with adjustment for age, gender and nodule size; the analysis was performed with Bethesda category 6 as reference. Two

Table 1. Distribution of Bethesda categories in 2065 thyroid nodules confirmed as conventional papillary thyroid carcinomas

Bethesda category	No. of patients
1	26 (1.26%)
2	30 (1.45%)
3	111 (5.38%)
4	4 (0.19%)
5	657 (31.82%)
6	1237 (59.90%)