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● *Original Contribution*

COMPARISON OF ULTRASOUND, PATHOLOGIC AND PROGNOSTIC CHARACTERISTICS OF THE FOLLICULAR VARIANT OF PAPILLARY THYROID CANCER ACCORDING TO FINE-NEEDLE ASPIRATION CYTOLOGY

Jieun Koh,* Eun-Kyung Kim,* Ji-Ye Kim,† Jin Young Kwak,* Jung Hyun Yoon,* and Hee Jung Moon*

*Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; and †Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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Abstract—The aim of the study described here was to compare ultrasound features, pathologic characteristics and prognoses of the follicular variant of papillary thyroid carcinoma (FVPTC) according to cytology results. Eighty-seven FVPTCs were classified according to the first cytology results as the surgery group (n = 66, follicular neoplasm/Hürthle cell neoplasm, suspicious for malignancy and malignancy) and the indeterminate group (n = 21, non-diagnostic and benign), for whom the management was follow-up. The indeterminate group had a longer mean interval to surgery ($p = 0.020$) and larger tumor size ($p = 0.018$). More tumors were assessed as probably benign in the indeterminate group than in the surgery group ($p < 0.001$). Extrathyroidal extension and lymph node metastasis did not significantly differ between the two groups, and no patient had a recurrence (mean follow-up interval: 54.9 ± 16.9 mo). The indeterminate group exhibited more probably benign features and larger size on ultrasound, with surgery being performed at a later date. However, aggressive pathologic characteristics and tumor recurrence did not significantly differ between the two groups. (E-mail: artemis4u@yuhs.ac)

Key Words: **Fine-needle aspiration, Follicular variant of papillary thyroid cancer, Cytology, Ultrasound, Prognosis.**

INTRODUCTION

The follicular variant of papillary thyroid cancer (FVPTC) is a tumor with a follicular pattern with nuclear features of papillary thyroid cancer (PTC) such as nuclear grooves, intra-nuclear cytoplasmic inclusions and powdery chromatin (Kesmodel et al. 2003; Rosai 2010). FVPTC compromises 10–15% of all PTCs and is the second most common type of PTC observed after conventional PTC (Kesmodel et al. 2003; Yoon et al. 2016). Lymph node metastasis or extrathyroidal extension are less frequent in FVPTC than in conventional PTC, but are more frequent than in follicular thyroid cancer (FTC), with survival rates being similar to those of conventional PTC (Lang et al. 2006; Yu et al. 2013; Zidan et al. 2003). FVPTC can be classified into infiltrative FVPTC and encapsulated FVPTC on the basis of tumor encapsulation; the infiltrative type of FVPTC is similar to conventional PTC, whereas the encapsulated type is similar to follicular neoplasm (Liu et al. 2006). Different prognoses and clinical behavior have been reported for each encapsulation type (Liu et al. 2006; Vivero et al. 2013).

In most studies, FVPTC has exhibited a relatively benign appearance on ultrasound (US) similar to that of follicular neoplasm (Baloch et al. 2002; Kim et al. 2009; Ozdemir et al. 2011; Rago et al. 2007), but in one study, the majority of FVPTCs had suspicious US features (Yoon et al. 2008). Diagnosing FVPTC by fine-needle aspiration (FNA) can be difficult, because there are no universal diagnostic criteria for diagnosing FVPTC by FNA. The sensitivity of FNA for diagnosing FVPTC has been reported to range from 25% to 37% in previous studies (Kesmodel et al. 2003; Shih et al. 2005), while definitive pre-operative diagnosis of conventional PTC has reached 94% (Ustun et al. 2014). Inter-observer variability is also an issue because diagnosing

Address correspondence to: Hee Jung Moon, Department of Radiology, Research Institute of Radiological Science, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, Republic of Korea. E-mail: artemis4u@yuhs.ac

FVPTC has been reported to be dependent on the pathologists' ability to detect nuclear features of PTC (Chan 2002; Lloyd et al. 2004; Renshaw and Gould 2002). In FVPTC, indeterminate US-FNA results are relatively common (Kim et al. 2009). To our knowledge, no study has assessed the differences in US features, surgical pathology and prognosis on the basis of FNA results in FVPTC patients. Therefore, we investigated whether US features and pathologic and prognostic characteristics of FVPTC differ according to the management recommendations based on the first FNA results.

METHODS

The institutional review board approved this retrospective study and waived the requirement for informed consent.

Study population

From March 2008 to November 2009, 13,559 thyroid nodules in 10,960 patients underwent US-guided FNA (US-FNA) at our institution (a tertiary referral center). Among these, 9667 nodules underwent US-FNA for the first time. During this period, 107 patients were confirmed as having FVPTC by surgery after US-FNA results of non-diagnostic (n = 16), benign (n = 9), follicular neoplasm/Hürthle cell neoplasm (n = 4), suspicious for malignancy (n = 27) and malignancy (n = 51). Of 107 patients, 19 with co-existing conventional PTC and one with completion surgery were excluded. Finally, 87 patients with FVPTCs only were included. The mean age of the patients was 50.4 ± 10.4 y (range: 25 to 75 y); 75 were women, and 12 were men. The mean size of the index tumor on US was 12.5 ± 11.4 mm (range: 3–59 mm). Thirty-seven tumors (42.5%) were ≥10 mm and 50 (57.5%) were <10 mm on US. There was no single case of distant metastasis at the time of US-FNA.

US and US-FNA

Gray-scale US evaluation of the thyroid nodules was performed with a 5- to 12-MHz linear transducer (iU22, Philips Medical Systems, Bothell, WA, USA) or a 6- to 13-MHz linear transducer (EUB-7500, Hitachi Medical, Tokyo, Japan). US examinations and US-FNA were performed by 10 board-certified radiologists dedicated to thyroid imaging and with 1 to 15 y of experience in thyroid imaging. The radiologists recorded the location of each nodule that underwent US-FNA as being in the right or left, and the upper third, mid-third or lower third on longitudinal images. Nodule size and US features were also recorded with respect to composition, echogenicity, margin, calcification and shape. Internal composition of the nodules was recorded as solid or not solid. Echogenicity of the nodules was recorded as hyper-, iso-, hypo- and marked hypo-echogenicity (marked hypo-echogenicity compared with the surrounding strap muscle). Margins of the nodules were assessed as well circumscribed or not well circumscribed (microlobulated and irregular). Shape of the nodules was classified as taller than wide or wider than tall. Calcification in the nodules was classified as microcalcifications (including mixed micro- and macrocalcifications), macrocalcifications and no calcification. Suspicious US features were marked hypo-echogenicity, a not well circumscribed margin, taller than wide shape and presence of microcalcifications (Kim et al. 2002). When one or more suspicious US features were observed, thyroid nodules were finally assessed as suspicious malignant, whereas those without any suspicious US features were assessed as probably benign. US-FNA was performed on the suspicious malignant nodules. In cases with no suspicious malignant nodules, US-FNA was performed on the largest probably benign nodule. US-FNA was performed using a 23-gauge needle attached to a 2-mL disposable plastic syringe at least two times with the free-hand technique. Aspirates were smeared and placed immediately into 95% alcohol for Papanicolaou staining. The remaining aspirate was rinsed with saline for cell blocking. Cytopathologists were not on site during the procedures, and the decision to perform special staining was made individually by the reading cytopathologist.

During the study period, a five-tier categorization system was used (Suen et al. 1997). US-FNA cytology was classified as "diagnostic" or "non-diagnostic." The nodule was classified into the "diagnostic" group if there was a minimum of six groups of well-preserved thyroid cells, with at least 10 cells per group, and the "diagnostic" nodule was further classified into four subgroups: benign, follicular neoplasm/Hürthle cell neoplasm, suspicious for malignancy and malignancy. The Bethesda system has been used since December 2009 in our institution (Cibas and Ali 2009), and a portion of the repeat US-FNAs were performed after this date. For US-FNAs performed after December 2009, cytology was reported with the Bethesda system using one of six categories: non-diagnostic or unsatisfactory, benign, atypia of undetermined significance or follicular lesion of undetermined significance, follicular neoplasm or suspicious for a follicular neoplasm, suspicious for malignancy and malignant.

Operation and post-operative surveillance

Total thyroidectomy was performed on 44 patients (50.6%), and lobectomy was performed on 43 patients (49.4%). Fourteen patients with extrathyroidal extension or lymph node metastasis underwent post-operative ^{131}I radioiodine ablation treatment as well. For