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● *Original Contribution*

ULTRASONOGRAPHIC DIFFERENTIATION BETWEEN NODULAR HYPERPLASIA AND NEOPLASTIC FOLLICULAR-PATTERNED LESIONS OF THE THYROID GLAND

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Abstract—We evaluate the gray-scale ultrasonographic characteristics that differentiate between nodular hyperplasia (NH) and neoplastic follicular-patterned lesions (NFPLs) of the thyroid gland. Ultrasonographic features of 750 patients with 832 thyroid nodules (NH, n = 361; or NFPLs, follicular adenoma, n = 123; follicular carcinoma, n = 159; and follicular variant papillary carcinoma, n = 189) were analyzed. Except for echogenicity, over two-thirds of the cases of NH and NFPLs share the ultrasonographic characteristics of solid internal content, a well-defined smooth margin and round-to-ovoid shape. Independent predictors for NH were non-solid internal content (sensitivity 27.1%, specificity 90.2%), isoechogenicity (sensitivity 69.5%, specificity 63.5%) and an ill-defined margin (sensitivity 18.8%, specificity 94.5%). Independent predictors for NFPLs were hypoechogenicity (sensitivity 60.5%, specificity 70.4%), marked hypoechogenicity (sensitivity 2.8%, specificity 99.4%) and taller-than-wide shape (sensitivity 6.6%, specificity 98.1%). Although NH and NFPLs commonly share ultrasonographic characteristics, non-solid internal content and ill-defined margin are specific to NH and marked hypoechogenicity and taller-than-wide shape are specific to NFPLs. (E-mail: jihnkim@gmail.com)

Key Words: **Ultrasonography, Thyroid, Nodular Hyperplasia, Follicular-patterned lesion, Follicular adenoma, Follicular carcinoma, Follicular variant papillary carcinoma.**

INTRODUCTION

Follicular-patterned lesions (FPLs) of the thyroid gland predominantly exhibit follicular-patterned growth, or thyroid follicles with a central lumen containing variable amounts of colloid on light microscopy (Baloch and Livolsi 2002, 2007). The FPL class of thyroid nodules is composed of nodular hyperplasia (NH) and neoplastic follicular-patterned lesions (NFPLs), which include follicular adenoma (FA), follicular carcinoma (FC) and follicular variant papillary carcinoma (FVPC). Follicular variant medullary carcinoma and hybrid tumor are also included in the FPL class, but are very rarely reported (Baloch and Livolsi 2002; DeMay 2000; Faquin 2009; LiVolsi and Baloch 2011; Suster 2006; Wu et al. 2012).

NH is the most commonly encountered pathology among thyroid nodules, and differentiation of NH from NFPLs may prevent unnecessary surgery in many patients with thyroid nodules (DeMay 2000). Within the NFPL group, FC is the second most common type of thyroid malignancy, accounting for approximately 10% of all thyroid malignancies, and FVPC is the second most common variant of papillary carcinoma (PC), after conventional PC, accounting for 11.8% to 41% of all PC cases (Baloch and LiVolsi 2007; Lang et al. 2006; Zidan et al. 2003). FPL is the most commonly encountered type of thyroid fine needle aspiration (FNA) specimen (Faquin 2009), but great difficulties have been reported in the cytologic differentiation between NH and NFPL as well as in the differentiation of NFPL sub-groups such as FA and FC (Baloch and Livolsi 2002; DeMay 2000; Faquin 2009; LiVolsi and Baloch 2011; Suster 2006; Wu et al. 2012).

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Ultrasonography (US) is a mainstay of assessment, along with FNA, of thyroid nodules (Gharib et al. 2010; Haugen et al. 2016). Recent studies have reported that US can have an important complementary role in guiding management decisions for patients with thyroid nodules of indeterminate cytology (Gweon et al. 2013; Kim et al. 2011; Lee et al. 2013b; Yoo et al. 2014). However, current well-established US criteria for identifying malignant thyroid nodules have many pitfalls when applied for the differentiation of the FPL type. In a meta-analysis by Brito et al. (2014), the majority (84%) of the malignant tumor cases in 31 cohort studies enrolling adults with thyroid nodules was PC, and benign nodules that were used as reference standards in the included studies were not solely identified by histopathologic diagnosis after surgery, but also by core biopsy, repeated FNA and follow-up US. Although many of the benign nodules in the studies might have been NH, there is no way to know how many NFPLs were erroneously included among them.

Several authors have investigated the US characteristics of various subsets of FPL among a limited numbers of patients. However, there have been no comparative imaging studies that have included all subtypes of FPL and that intended to differentiate between NH and NFPLs (Bonavita et al. 2009; Jeh et al. 2007; Kim et al. 2009; Lai et al. 2013; Moon et al. 2009; Ozdemir et al. 2011; Seo et al. 2009; Sillery et al. 2010; Yoon et al. 2008, 2014; Zhang and Hu 2014). In this study, we have evaluated a large set of surgically confirmed FPLs from a consecutive cohort of patients with the purpose of identifying the gray-scale US characteristics that differentiate between NH and NFPLs of the thyroid gland.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board, and informed consent was waived.

Patient selection

From January 2007 to December 2011, a total of 7866 consecutive patients underwent total thyroidectomy or lobectomy at a tertiary referral hospital. Among them, 1008 patients who received a diagnosis of NH, FA, FC or FVPC using the electronic medical records and pathology databases of our hospital were identified. Subsequently, we excluded 258 patients for the following reasons: (i) no available pre-operative thyroid US (n = 45); (ii) an interval of >6 mo between surgery and the most recent pre-operative US (n = 49); (iii) poor quality of US images of target nodules (n = 91); and (iv) discrepancies in the descriptions of the location of target nodules between US and pathology reports (n = 73). Finally, a total of 750 patients (614 women and 136 men) with 832 nodules (361 NH, 123 FA, 159 FC and 189 FVPC) were included. No patient was diagnosed with follicular variant medullary carcinoma or hybrid tumor in our hospital during the study period. We combined FA, FC and FVPC in our analysis and designated them as NFPLs. We also combined FC and FVPC and designated them as malignant follicular-patterned lesions (MFPLs). The mean patient age was 48.7 y ± 13.4 y and the mean interval between surgery and the most recent pre-operative US was 42.1 d ± 48.9 d.

Ultrasound examination technique

Three US machines (Accuvix XQ, Medison Co. Ltd, Seoul, Korea; IU 22, Philips Medical System, Bothel, WA, USA; and LOGIQ9, GE Medical Systems, Milwaukee, WI, USA) with a high-frequency linear transducer (7.5–15 MHz) were used for US examinations. Faculty radiologists (C.H.S., D.G.N., J.-H.K. and S.H.C., with 19 y, 13 y, 8 y and 6 y of experience in performing thyroid US, respectively) performed the examination or supervised the examination performed by board-certified radiologists and residents who were participating in the thyroid radiology training program. Representative images of the thyroid nodules in both transverse and longitudinal planes were stored in picture archiving and communication systems.

Retrospective imaging analyses

Two radiologists (D.G.N. and J.-H.K.) reviewed all of the US images in the digital imaging and communications in medicine format. The reviewers were blinded to the clinical history of patients and to the final pathology diagnosis of the nodules. Final decisions were reached by consensus.

In accordance with the consensus statement and recommendations of Moon et al. (2011), we evaluated nodule size, internal content, echogenicity, margin and shape, and we noted the presence of calcification (microcalcification, macrocalcification and rim calcification), hypoechoic halo, spongiform appearance and colloid-like feature in the nodules. We selected the longest diameter in either the transverse or longitudinal plane to describe nodule size. The internal content of each nodule was categorized as solid (<10% cystic) or non-solid (≥10% cystic) according to the ratio of the cystic portion to solid portion. The echogenicity of a nodule was determined by comparisons among the solid portion of the nodule, the thyroid parenchyma and the strap muscles, and nodules were defined as hyperechoic when they were more echogenic than the normal thyroid parenchyma, isoechoic when they had the same echogenicity as the normal thyroid parenchyma, hypoechoic when they were more hypoechoic than the normal thyroid parenchyma and markedly hypoechoic when they were