



● Original Contribution

REVISED VALUE OF CONTRAST-ENHANCED ULTRASOUND FOR SOLID HYPOECHOIC THYROID NODULES GRADED WITH THE THYROID IMAGING REPORTING AND DATA SYSTEM

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Abstract—The use of ultrasound in differentiation of benign and malignant solid hypo-echoic thyroid nodules is a dilemma in clinical practice. The aim of this study was to investigate the revised value of contrast-enhanced ultrasound (CEUS) for differentiating solid hypo-echoic thyroid nodules using the Thyroid Imaging Reporting and Data System (TI-RADS). The study included 135 patients with 135 nodules confirmed by fine-needle aspiration and/or surgery. Every nodule underwent both conventional US and CEUS. Binary logistic regression analysis for conventional US features revealed that irregular shape, microcalcification and height greater than width were significant malignant predictive features. Binary logistic analysis for CEUS features indicated that hetero-enhancement, slow wash-in, an ill-defined enhancement border and fast wash-out were significantly associated with malignancy. The areas under the curve of the TI-RADS, CEUS and the combination were 0.806, 0.934 and 0.950, respectively. CEUS is a potentially useful tool in the differentiation of solid hypo-echoic thyroid nodules. (E-mail: fang-nie@163.com) © 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Contrast-enhanced ultrasound, Solid hypo-echoic thyroid nodules, Thyroid Imaging Reporting and Data System.

INTRODUCTION

Accurate qualitative diagnosis of thyroid nodules is important for determination of clinical treatment strategies and estimation of prognosis. The Thyroid Imaging Reporting and Data System (TI-RADS) classification (Horvath et al. 2009; Kwak et al. 2011; Park et al. 2009) identifies benign and malignant thyroid nodules through a comprehensive analysis of nodule morphologic characteristics. Additionally, this classification provides a standard for the diagnosis of thyroid nodules. However, improvements can be made in its application for the differentiation of benign and malignant thyroid nodules. A solid hypo-echoic feature is an important ultrasound (US) feature that suggests malignancy among thyroid nodules (Haugen et al. 2016). However, not all solid hypo-echoic thyroid nodules are malignant (Anil et al. 2011). A recent study revealed that 44.5% of benign thyroid nodules had a solid hypo-echoic feature (Ha et al. 2016). Therefore, the accurate differentiation of solid hypo-echoic thyroid nodules on US

is a dilemma in clinical practice. A tool with high positive predictive value for malignancy is desired.

Numerous studies have reported that contrast-enhanced ultrasound (CEUS) has high sensitivity and specificity in detecting malignant thyroid nodules (Hornung et al. 2012; Nemec et al. 2012; Wendl et al. 2016; Zhang et al. 2016). However, CEUS is not widely used in clinical practice to manage thyroid nodules. A major reason is that no final assessment about thyroid tumors with respect to the diagnostic accuracy of CEUS exists, in line with the current non-liver guidelines (Piscaglia et al. 2012). Therefore, the aim of this study was to investigate the revised value of CEUS for differentiating solid hypo-echoic thyroid nodules using TI-RADS and to determine whether diagnostic accuracy has improved.

METHODS

Patients

Patients with thyroid nodules were prospectively enrolled between October 2015 and November 2016. Patients with solid hypo-echoic thyroid nodules suspected of being malignant on conventional US or nodules that required confirmation of their nature were enrolled. The management

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plan for patients included fine-needle aspiration (FNA) and surgery subsequent to the examination. Patients were followed up to determine the pathologic diagnosis. All patients referred for FNA were examined using CEUS. The exclusion criteria were as follows: (i) absence of a pathologic diagnosis; (ii) FNA result indicating category I, III, IV or V according to the Bethesda classification (Cibas and Ali 2009); and (iii) presence of thyroid nodules that were too large to compare with normal parenchyma. Finally, a total of 135 nodules in 135 patients (32 male and 103 female patients; mean age, 49 ± 11 y; age range, 23–28 y) were included. The thyroid lesions collected had a maximum diameter of 0.5–3.4 cm (mean, 1.2 ± 0.6 cm). Of the 135 nodules, 5 were in the isthmus of the thyroid, 54 were in the left lobe and 76 were in the right lobe. Of the 135 patients, 71 had a single nodule and 64 had multiple nodules. Additionally, 16 patients had undergone both FNA and surgery at our institution, and 119 had undergone only FNA.

This study was approved by the institutional review board of our institution, and all patients signed an informed consent form.

Conventional US

Conventional US images of thyroid nodules were obtained using an iU22 scanner (Phillips Medical Systems, Bothell, WA, USA) equipped with a 5- to 12-MHz linear probe by two radiologists who were board certified and had at least 4 y of experience in thyroid US. The patient was placed on a bed in the supine position and was fully exposed. Conventional US images of the thyroid nodule were acquired by carefully scanning the thyroid and adjacent tissues both transversely and longitudinally. The nodule's size was defined by the maximal diameter on US. The number and location of the nodules were also recorded. The radiologists selected nodules with suspicious malignant features, such as hypo-echogenicity, microcalcification, an irregular margin and height greater than width on transverse view, for further evaluation (Haugen et al. 2016). Hypo-echogenicity was described as mild or marked using the echogenicity of normal thyroid parenchyma and the anterior neck muscle as a reference. Shape was described as regular or irregular. The nodule margin was described as well defined or poorly defined. Calcification was categorized as microcalcification (<2 mm in diameter without an acoustic shadow), macrocalcification (≥ 2 mm in diameter with acoustic shadows), rim calcification or no calcification (Xu et al. 2014). Height and width were categorized as height greater than width or width greater than height. If multiple nodules were present, the most suspicious nodule was targeted. The TI-RADS classification (Kwak et al. 2011) was used to evaluate and classify every thyroid nodule. The machine settings were optimized to obtain optimal US images, and then, the images were stored in the internal hard disk of the

instruments for further analysis. All nodules were TI-RADS class >3 and were considered suspicious for malignancy.

CEUS and analysis

Contrast-enhanced ultrasound examination was performed with the same instrument used for conventional US, with a 3- to 9-MHz linear probe by a radiologist with 6 y of experience in CEUS. CEUS was performed using a low mechanical index (0.10) to minimize microbubble destruction and artificial signal loss. The plane with the maximal nodular size and appropriate amount of surrounding parenchyma was selected in every nodule for CEUS. Patients were instructed to stop swallowing and to breathe calmly during the entire process. The contrast agent was mixed with 5 mL of saline until a homogeneous mixture was obtained. Then, 1.8 mL of the suspension was quickly pushed into the peripheral vein with a probe, and the body position was unchanged. The timer on the US machine was started at the time of contrast medium injection. Each contrast imaging acquisition lasted at least 3 min, and the process was preserved in the US instrument.

The CEUS images were quantitatively analyzed using QLAB software. A single region of interest (ROI) was selected manually, and it contained the whole nodule. A similar ROI area was selected from adjacent normal thyroid tissue as a control (Figs. 1–3). Then, time–intensity curves (TICs) using the LDRW-WIWO (local density random walk wash-in wash-out) method were acquired. In the TICs, the following characteristics of thyroid nodules were evaluated (Hu et al. 2015):

1. Rise time (RT): RT (nodule) $<$ RT (normal) indicates rapid filling-in, otherwise slow filling-in.
2. Time to peak (TP): TP (nodule) $<$ TP (normal) indicates rapid filling-in, otherwise slow filling-in.
3. Wash-in slope (WIS): WIS (nodule) $<$ WIS (normal) indicates slow wash-in, otherwise rapid wash-in.
4. Mean transit time (MTT): MTT (nodule) $<$ MTT (normal) indicates fast wash-in, otherwise slow wash-in.
5. Time from peak to one-half (TPH): TPH (nodule) $<$ TPH (normal) indicates rapid wash-out, otherwise slow wash-out.
6. Peak intensity (PI): PI (nodule) $<$ PI (normal) indicates hypo-enhancement, otherwise hyper-enhancement.
7. Area under the curve (AUC): AUC (nodule) $<$ AUC (normal) indicates hypo-enhancement, otherwise hyper-enhancement.
8. Peaking time echo standard deviation (PES): PES (nodule) $<$ PES (normal) indicates homo-enhancement, otherwise hetero-enhancement.

Finally, we obtained the following semiquantitative parameters: (i) enhancement shape (hetero-enhancement

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