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● *Original Contribution*

ROLE OF CONTRAST-ENHANCED ULTRASOUND IN DIAGNOSIS OF THYROID NODULES IN ACOUSTIC RADIATION FORCE IMPULSE "GRAY ZONE"

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Abstract—The aim of this study was to evaluate the clinical value of contrast-enhanced ultrasound (CEUS) in the diagnosis of thyroid nodules in the acoustic radiation force impulse (ARFI) "gray zone" (the shear wave velocity is in the range 2.5–3 m/s). ARFI was performed before thyroidectomy in 70 patients with 200 thyroid nodules, and then CEUS was performed in 40 thyroid nodules in the "gray zone." The accuracy of ARFI for the 200 thyroid nodules was 82% (164/200). The accuracy of ARFI for the 40 "gray zone" thyroid nodules was 70% (28/40), whereas the accuracy of CEUS for the "gray zone" thyroid nodules was 90% (36/40). There was a significant difference in accuracy ($p < 0.05$). CEUS has better accuracy for thyroid nodules in the ARFI "gray zone." CEUS supplemented ARFI in differential diagnosis of benign and malignant thyroid nodules. (E-mail: ultrasound_drchen@163.com) © 2017 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Contrast-enhanced ultrasound, Acoustic radiation force impulse, Shear wave elastography imaging, Thyroid nodules.**

INTRODUCTION

Thyroid nodules are a common clinical problem, and the incidence of thyroid cancer has increased significantly in recent decades (Stewart and Wild 2014). Thyroid lesions are very common and are found in 3%–7% of adults by palpation (Gharib et al. 2010) and in 19%–76% by high-resolution ultrasound (US) (Cooper et al. 2006; Ferraz et al. 2011). Most thyroid nodules are benign, and very few represent cancer (5%) (Rago et al. 1998). Conventional US is the primary non-invasive method used for diagnosing thyroid lesions because of its low cost and wide availability. Presence of calcification, hypoechogenicity, irregular margins, absence of a halo and intra-nodular vascularity in the sonographic image are the key features associated with an increased risk of malignancy (Gharib et al. 2010). However, no sonographic feature has both a high sensitivity and a high positive predictive value (PPV) for thyroid cancer (Zhang et al. 2014a, 2014b). A classic criterion of malignancy is hardness on palpation, and with the introduction of elastography, an assessment of tissue stiffness has become available.

Acoustic radiation force impulse (ARFI) imaging represents a new technology for the quantification of tissue elasticity. A meta-analysis of 13 studies yielded a mean sensitivity of 86% and mean specificity of 89% for detecting malignant nodules (Dong et al. 2015).

In ARFI imaging, tissue is mechanically stimulated using short-duration (262 μs) acoustic pulses. (This pulse duration appears to be specific to the system being used and not to the entire field of ARFI.) The acoustic pulses generate localized tissue displacements within the region of interest (ROI). The displacements induce a lateral shear wave propagation that is tracked using multiple laterally positioned US "tracking" beams. By measurement of the time to peak displacement at each lateral location, the shear wave velocity (V_s, expressed in m/s) within the tissue can be reconstructed. The shear wave propagation velocity is proportional to the square root of tissue elasticity (Nightingale et al. 2002). The stiffer the tissue is, the faster the shear wave propagates.

Most studies in the meta-analysis reported that the V_s cutoff was in the range 2.5–3 m/s, which is called the "gray zone." In this range, it is difficult to perform differential diagnosis of thyroid nodules by stiffness measurement alone (Zhan et al. 2015a, Zhan et al. 2015b). Relatively, thyroid nodule V_s values <2.5 m/s indicate soft and probably benign nodules ("white zone"), and V_s values >3 m/s indicate hard and probably malignant nodules ("black zone").

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The aim of the present study was to evaluate whether contrast-enhanced ultrasound (CEUS) can be performed with reliable results for thyroid nodules in the "gray zone." Although we had reported a similar point in a Chinese journal published earlier (Zhan et al. 2015a, Zhan et al. 2015b), we believe a further discussion here would be in order, not only for the accuracy of CEUS in these thyroid nodules, but also for ultrasonic disposal and the rational combination of CEUS and ARFI.

METHODS

Patients

Informed consent was obtained from all patients, and the study was performed in accordance with the ethical guidelines of the Helsinki Declaration and approved by the local ethics committee. From November 2014 to May 2016, 200 thyroid nodules in 70 patients (16 men and 54 women) were enrolled in the study. The mean age of the patients examined was 49.6 ± 12.8 y (range: 28–70 y). The median size of the masses was 0.8 × 0.6 × 0.9 cm (range: 0.6 × 0.5 × 0.6 to 2.0 × 1.2 × 1.5 cm).

The inclusion criteria for CEUS were as follows: (i) nodules must appear solid or almost solid (<25% cystic) on conventional US; (ii) thyroid nodules must be classified as Thyroid Imaging Reporting and Data System (TI-RADS) category 4 on conventional US; (iii) nodules must be >0.5 cm and <1.0 cm (with nodules <0.5 cm, it is difficult to maintain the same imaging sections during CEUS examination because of arterial pulsation and breathing; the CEUS patterns of malignant nodules >1.0 cm differ from those of smaller nodules); (iv) thyroid nodules must be in the "gray zone" (3 m/s > V_s > 2.5 m/s). The exclusion criteria were a shear wave velocity appearing as V_s = X.XX cm/s and a dominance of cystic nodules. Finally, a total of 40 nodules were included.

Conventional ultrasound (B-mode and Doppler)

All ultrasonography examinations were performed with a 9-MHz transducer (Acuson S2000, Siemens, Erlangen, Germany). The patients were positioned in a supine position with dorsal flexion of the head. The US examination was performed by experienced examiners. Thyroid nodules were evaluated for size, volume, echogenicity, echotexture, presence or absence of halo sign and presence or absence of microcalcification. Classification as TI-RADS category 4 was carried out independently by two reviewers (J.Z. and L.C.) on the basis of five US suspicious features (Kwak et al. 2011). Discrepancies were adjudicated by discussion with a third reviewer (X.H.D.).

After B-mode US, color Doppler and duplex imaging were performed. The vascular distribution of thyroid nodules was classified into three types (Rago et al. 1998): type I, absence of blood flow; type II, perinodular and absent or slight intra-nodular blood flow; and type III, marked intranodular and absent or slight perinodular blood flow. Other criteria included perforating branches (presence or absence) and a resistance index (RI) ≥0.75 or <0.75 (De Nicola et al. 2005) (RI = PSV−EDV/PSV, where PSV = peak systolic velocity and EDV = end-diastolic velocity).

Acoustic radiation force impulse

Acoustic radiation force impulse imaging was performed in all patients using a Siemens Acuson S2000 US system with a 9 L4 transducer by two operators (each had at least 5 y of experience in conventional US examination with more than 200 ARFI measurements performed). Participants were in a supine position with the neck hyperextended and were holding their breath, avoiding swallowing. For each nodule, five successful measurements were performed with the ROI, and the median value was recorded.

Contrast-enhanced ultrasound examination

All CEUS imaging of thyroid nodules was performed by two experienced clinical US physicians (J.Z. and X.H.D.) with more than 5 y of experience in US thyroid examination. After the conventional ultrasonography examination, the largest plane of the nodule was selected before the transducer was switched to the CEUS mode. The focus zone was always placed at the bottom level of the nodule being examined to adhere to the comparability principle (Ma et al. 2014). CEUS was performed using a low mechanical index (MI < 0.10) to minimize microbubble destruction and artificial signal loss. Term US contrast agent (SonoVue, Bracco International, Milan, Italy) was injected into an antecubital vein with a bolus of 2.0 mL *via* a 20-gauge cannula followed by a 5-mL saline flush. Although the contrast enhancement process and timer on the US machine were started, real-time dynamic images that lasted at least 2 min were digitally stored on a computer-based workstation. During the process, the patient was always asked to hold his or her breath and avoid swallowing at the same time.

On CEUS, the thyroid nodules were evaluated relative to a normal thyroid parenchyma. Microbubble arrival time/degradation time was classified as earlier or meantime/later; the entrance mode on CEUS was classified as centripetal or non-centripetal; the echo intensity at peak enhancement was classified as hyper- or iso-enhancement/hypo-enhancement; the homogeneity of enhancement was classified as homogeneous or heterogeneous; and relative washout time was classified as earlier or not earlier.

During the post-processing analysis, the operator manually drew an ROI covering the tissue that had to be studied, and a color map was automatically generated by the system. Then, further and smaller ROIs of similar size were hand drawn on the color map within the tumor. Finally,