Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–7, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.04.026

● *Original Contribution*

LOGISTIC REGRESSION ANALYSIS OF CONTRAST-ENHANCED ULTRASOUND AND CONVENTIONAL ULTRASOUND CHARACTERISTICS OF SUB-CENTIMETER THYROID NODULES

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(*Received* 16 *October* 2014; *revised* 25 *April* 2015; *in final form* 28 *April* 2015)

Abstract—The purpose of the study described here was to determine specific characteristics of thyroid microcarcinoma (TMC) and explore the value of contrast-enhanced ultrasound (CEUS) combined with conventional ultrasound (US) in the diagnosis of TMC. Characteristics of 63 patients with TMC and 39 with benign sub-centimeter thyroid nodules were retrospectively analyzed. Multivariate logistic regression analysis was performed to determine independent risk factors. Four variables were included in the logistic regression models: age, shape, blood flow distribution and enhancement pattern. The area under the receiver operating characteristic curve was 0.919. With 0.113 selected as the cutoff value, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 90.5%, 82.1%, 89.1%, 84.2% and 87.3%, respectively. Independent risk factors for TMC determined with the combination of CEUS and conventional US were age, shape, blood flow distribution and enhancement pattern. Age was negatively correlated with malignancy, whereas shape, blood flow distribution and enhancement pattern were positively correlated. The logistic regression model involving CEUS and conventional US was found to be effective in the diagnosis of sub-centimeter thyroid nodules. (E-mail: yuxinjiangxh@163.com) © **2015 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology**

Key Words: **Thyroid microcarcinoma, Ultrasonography, Contrast-enhanced ultrasound, Logistic models.**

INTRODUCTION

With advancements in technology and wide use of ultrasound (US), the detection of sub-centimeter nodules in the general population has greatly increased (Brander et al. 1991; Ezzat et al. 1994). The probability of malignancy in sub-centimeter thyroid nodules is not lower than that in supra-centimeter nodules (Berker et al. 2008; Papini et al. 2002; Sharma et al. 2011). About 11% of papillary thyroid microcarcinomas (TMCs) exhibit local invasion, lymph node metastasis or distant metastasis (Baloch and LiVolsi 2006; Hedinger et al. 1989). The American Thyroid Association and the European Thyroid Association guidelines recommend that nodules <1 cm in diameter should be considered for fine-needle aspiration biopsy (FNAB) if there are suspicious US findings, such as a round, solid, hypo-echoic nodule with microcalcifications or an irregular border, or a personal history of familial thyroid cancer or head and neck irradiation (Cooper et al. 2009; Pacini et al. 2008). Consequently, identification of nodules that do not require FNAB is an important clinical problem.

Certain US features, such as many diffuse calcifications, rim calcifications, a purely solid structure and a taller-than-wide shape, can be used to accurately stratify the risk of malignancy and to determine the need for US-guided FNAB (Sharma et al. 2011). Currently, features significantly associated with malignancy in sub-centimeter nodules include marked hypo-echogenicity, solid composition, microlobulated or irregular margins, microcalcifications, macrocalcifications, rim calcifications, many diffuse calcifications, taller-than-wide shape, posterior acoustic shadowing and nodular vascular spots. Not all studies report the same set of risk factors (Berker et al. 2011; Kim et al. 2013; Kwak et al. 2009; Papini et al. 2002; Sharma et al. 2011).

Accuracy in the diagnosis of thyroid nodules can be increased by combining contrast-enhanced ultrasound (CEUS) with conventional US (Hornung et al. 2012;

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Conflicts of interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Nemec et al. 2009; Zhang et al. 2010). To date, there have only been a few studies on the value of CEUS in the diagnosis of TMC. In the present study, conventional US and CEUS characteristics of 102 cases of subcentimeter thyroid nodules were analyzed to determine specific features of TMC and to explore the value of CEUS combined with conventional US in the diagnosis of TMC.

METHODS

This study was approved by the ethics committee of Peking Union Medical Hospital, and informed consent was obtained from all patients before CEUS. We retrospectively reviewed our database of patients who underwent conventional US and CEUS from November 2011 to December 2013. The inclusion criteria were: the presence of lesions of diameter ≤1 cm on conventional US and complete US, clinical and pathology data. Exclusion criteria included heart, lung, kidney or other vital organ dysfunction; severe allergies; unsuitability for or intolerance to intravenous injection of contrast agent; age <18 y; pregnancy; and lactation. A total of 102 thyroid nodules in 83 consecutive patients were included. Surgery was performed on 99 nodules, and three nodules underwent US-guided FNAB for the final pathologic diagnosis.

All sonographic examinations were performed using an IU22 scanner (Phillips Medical Systems, Bothell, WA, USA) equipped with an L12-5 transducer. Standard machine settings were used, with a mechanical index (MI) of 0.05–0.08, compression of 33–35 and dynamic spatial reconstructor (DSR) middle setting. Once set, the US parameters remained unchanged in each patient. The contrast medium used was SonoVue (BR1, Bracco Imaging, Milan, Italy), a sulfur hexafluoride-filled microbubble contrast agent encapsulated in a flexible phospholipid shell.

Patients were maintained in a supine position with the neck fully stretched. The thyroid gland and surrounding tissues and lymph nodes in the neck were scanned carefully using gray-scale and color Doppler US. Dynamic range, gain, depth and focal zone were adjusted to optimize image quality during the examination. The largest plane of the lesion in long axis was selected, and the transducer was switched to gray-scale harmonic CEUS mode. Because bubble disruption is related to depth and focal zone, the focus was always located deeper than the nodule being examined to minimize microbubble disruption.

With a 20- or 22-gauge peripheral intravenous cannula, SonoVue was injected intravenously as a bolus at a dose of 1.2 mL, followed by 2 mL of normal saline as a flush. Meanwhile, the timer on the US machine was started, and the imaging plane was kept as stable as possible. Each contrast imaging acquisition lasted ≥3 min after bolus injection and was digitally stored as raw data on a personal computer–based workstation connected to the US unit *via* a standard Ethernet link. The same procedures were repeated in the short axis.

Conventional US and CEUS images and cine clips were reviewed retrospectively by two radiologists (B.Z., with 15 y experience in thyroid US, and R.Z., with 5 y experience in thyroid US), who were blinded to the patients' clinical data and pathologic results. In cases of discrepancy between the two readers, a consensus was reached after discussion.

Conventional US characteristics include: shape, categorized as regular (round or oval) or irregular (angulation, burr, crablike or other irregular shape); border, categorized as well defined (distinct boundaries between the thyroid nodule and the surrounding parenchyma) or ill defined; halo, classified as a regular thin halo or no regular thin halo; echogenicity, classified as hypo-echoic (below the level of the surrounding parenchyma) or iso- or hyper-echoic (the same level or higher than the surrounding parenchyma); shortest axis-to-longest axis (S/L) ratio, classified as ≥1 (taller than wide in the transverse plane or taller than long in the longitudinal plane) or <1; calcification, classified as microcalcifications (fine or punctate or calcifications <1 mm in size inside solid components) or no microcalcifications (no calcification or coarse calcification); and blood flow distribution, classified as irregular blood flow (chaotically distributed, locally abundant blood flow, *i.e.*, asymmetry of the vascular spatial distribution, presence of a single nutrient vessel) or regular blood flow.

CEUS characteristics included: border, categorized as well defined (distinct boundaries between the thyroid nodule and the surrounding parenchyma) or ill defined at the time of maximal enhancement; shape, categorized as regular (round or oval) or irregular (angulation, burr, crablike, or other irregular shape) at the time of maximal enhancement; peak intensity, categorized as low, equal or high; arrival time (time from administration of contrast agent to appearance of first bubble in tumor), classified as earlier, simultaneous with or later than that for the surrounding parenchyma; peak time, classified as earlier, simultaneous with or later than that for the surrounding parenchyma; enhanced direction, classified as centripetal, centrifugal or diffuse; and enhancement pattern, classified as homogeneous, heterogeneous, ring-enhancing or non-enhancing (Zhang et al. 2010).

Statistical analyses were performed using the SPSS statistical package (Version 13.0, SPSS Chicago, IL, USA). Quantitative data are expressed as the mean ± standard deviation. Groups were compared using Student's *t*-test. The χ^2-test or Fisher's exact test was used to compare categorical data. In all cases, a *p* value