Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–9, 2017

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2017.07.010

● *Original Contribution*

ROLE OF CONTRAST-ENHANCED ULTRASOUND IN THE PRE-OPERATIVE DIAGNOSIS OF CERVICAL LYMPH NODE METASTASIS IN PATIENTS WITH PAPILLARY THYROID CARCINOMA

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(*Received* 13 *April* 2017; *revised* 4 *July* 2017; *in final form* 11 *July* 2017)

Abstract—The objective of this study was to prospectively evaluate the diagnostic accuracy of contrast-enhanced ultrasonography (CEUS) in differentiating between benign and metastatic cervical lymph nodes in patients with papillary thyroid cancer (PTC). Three hundred nineteen cervical lymph nodes (162 metastatic from PTC and 157 benign) were evaluated using conventional ultrasonography (US) and CEUS before biopsy or surgery. Metastatic lymph nodes more often manifested centripetal or asynchronous perfusion, hyper-enhancement, heterogeneous enhancement, perfusion defects and ring-enhancing margins than benign lymph nodes at pre-operative CEUS (all p values < 0.001). The area under the receiver operating characteristic curve (AUC) for the combination of conventional US and CEUS (0.983, 95% confidence interval [CI]: 0.971–0.994) was higher than that of conventional US alone (0.929, 95% CI: 0.899–0.958) and CEUS (0.911, 95% CI: 0.876–0.947). In conclusion, CEUS is a promising tool in conjunction with conventional US for the pre-operative prediction of metastatic cervical lymph nodes in patients with PTC. (E-mail: huangpintong@126.com) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Contrast-enhanced ultrasonography, Papillary thyroid cancer, Metastatic, Cervical lymph nodes.**

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer in children and adults, constituting up to 80% to 90% of all thyroid cancers (Sherman 2003). Despite the often indolent nature of PTC, cervical lymph node involvement is quite common. PTC involves metastasis to cervical lymph nodes in 30%–80% of patients (Noguchi et al. 1970; Sherman 2003). The presence of cervical lymph nodal metastases affects surgery type, extent of surgery and prognosis and was considered one of risk factors for local tumor recurrence and cancer-specific mortality (Ito et al. 2011; Roh et al. 2008). Therefore, the pre-operative diagnosis of cervical lymph node metastasis is very important.

Conventional ultrasonography (US) is the first-line method of examining cervical lymph nodes in patients with PTC. Metastatic lymph nodes commonly appear with hyper-echogenicity, calcifications, cystic necrosis, a round shape, peripheral or mixed vascularity and the absence of an echogenic hilum (Leboulleux et al. 2007; Lee et al. 2013; Rosário et al. 2005; Wu et al. 2012). Alternative diagnostic procedures include ultrasonography-guided fine-needle aspiration biopsy (US-FNAB). However, each of these various methods has its own limitations in the clinical diagnosis of lymph nodes and would benefit from the development of improved techniques (Leboulleux et al. 2007; Lee et al. 2013; Rosário et al. 2005; Wu et al. 2012). Improving the accuracy of pre-operative diagnosis of metastatic lymph nodes and reducing radical neck dissections remains a challenge.

Contrast-enhanced ultrasonography (CEUS) is a new technique that makes use of microbubble-based contrast agents to improve the echogenicity of blood; thus, improving visualization and assessment of tissue vascularity in real time (Burns et al. 2000; Cosgrove

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and Lassau 2010). Some studies had reported that CEUS may be a potential tool in differentiating between benign and malignant lymph nodes (Cui et al. 2013; Rubaltelli et al. 2004, 2007; Slaisova et al. 2013). However, fewer studies have involved cervical metastatic lymph nodes from thyroid cancer. Our previous study reported that CEUS may be a potential tool in detection of metastatic lateral lymph nodes and altered surgical procedures (Xiang et al. 2014). However, there was selection bias in our previous study because only patients with suspicious LNs found by conventional US were included. Therefore, patients without suspicious nodes found by conventional US were not enrolled, resulting in a relatively small sample of benign lymph nodes. This study focuses on the ultrasonographic features of cervical lymph nodes on CEUS and prospectively assesses the usefulness of CEUS in the prediction of metastatic central and lateral cervical lymph nodes in patients with PTC.

METHODS

Patients and study design

Written informed consent was obtained from all patients before their examination, and the local ethics committee and institutional review board approved this single-center prospective study. Five hundred seventy-three consecutive patients (425 females and 148 males; age range: 15–82 y; mean age: 49.5 ± 13.8 y) with thyroid nodules (Bethesda system ≥IV cytology) or previous history of thyroid cancer surgery scheduled for thyroidectomy or neck lymph node dissection between January 2014 and September 2016 were enrolled in this study. All eligible patients underwent conventional US and CEUS of the neck within 3 d before biopsy or surgery.

The inclusion criteria were the presence of a single or multiple cervical lymph nodes >0.5 cm in patients ≥18 y of age with thyroid nodules (Bethesda system ≥IV cytology) scheduled for thyroidectomy or with a previous history of thyroid cancer surgery. All cervical lymph nodes had a long-axis diameter of ≥1.0 or of ≥0.5 cm plus at least one of the following ultrasound features suspicious for malignant involvement: focal or diffuse hyper-echogenicity, presence of internal calcification, cystic aspect, round shape and chaotic or peripheral vascularity on Doppler US. All cervical lymph nodes were detected by conventional US and CEUS examination. Patients with lymphoma, metastasis not from PTC or tuberculous nodes confirmed by pathology were also excluded from this study.

The final diagnosis of malignant cervical lymph nodes was confirmed by one of the following criteria: (i) surgical pathologic results after thyroidectomy; (ii) gun biopsy; (iii) FNA cytology. Meanwhile, lymph nodes were considered benign if (i) the lymph node was diagnosed as benign on histology after surgery; (ii) the thyroid nodule was confirmed as benign on intra-operative frozen section without lymph node dissection and without other lymphadenopathy; (iii) gun biopsy or repeat FNA confirmed benignity; and (iv) there was a <20% increase in diameter and absence of conventional US features suspicious for malignancy (focal or diffuse hyper-echogenicity, presence of internal calcification, cystic aspect, round shape and chaotic or peripheral vascularity on Doppler US) on US performed after follow-up of at least 2 y after thyroidectomy for thyroid cancer. Finally, a total of 319 lymph nodes (162 metastatic and 157 benign lymph nodes) in 253 patients were included in this study.

Conventional US examination

Ultrasound investigations were performed by one operator (Y.R.H.) who had 15 y of experience with ultrasound diagnostics, using a MyLab Twice (Esaote, Genoa, Italy) machine equipped with an L523 (4–13 MHz) linear-array transducer for conventional US.

The cervical lymph nodes were divided into seven levels (I–VII) according to the American Joint Committee on Cancer Classification (Ying and Ahuja 2003). All selected cervical lymph nodes were assessed by gray-scale US for morphologic features in transverse and longitudinal sections. The short-axis and long-axis diameters in transverse view were measured, and the ratio of long-axis diameter to short-axis diameter (L/S ratio) was calculated. The margin of the lymph node was described as well-defined or ill-defined. A well-defined margin was well circumscribed with a smooth regular margin. An ill-defined margin was poorly circumscribed, blurred, irregular or with angular margins. Echogenicity with respect to the adjacent muscles was assessed and classified as hypoechoic, iso-echoic or hyper-echoic. Internal echo pattern was divided into heterogeneity or homogeneity. The presence or absence of an echogenic hilum, intra-nodal cystic necrosis or calcifications was also noted. On color Doppler US, vascularity in the lymph node was classified as follows: (i) avascular type—no flow signals detected inside the node; (ii) hilar type—a central hilar vessel with or without centrifugal branches, with no other segments originating from vessels other than the hilar vessel; (iii) peripheral type—vessels running along the capsule with or without centripetal branches; (iv) mixed type—concurrence of hilar and peripheral types or abundant and chaotic blood flow within the node (Nyman and O'Brien 2007).

CEUS examination

Contrast-enhanced US was performed using a MyLab Twice (Esaote, Genova, Italy) machine equipped with Contrast Tuned Imaging technology (CnTI). An L522 (3–9 MHz) linear array transducer was used with acoustic pressure of 60 kPa in each patient. The mechanical index (MI = 0.05–0.07) was selected automatically