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● *Original Contribution*

PREDICTIVE VALUE OF ESTIMATED TUMOR VOLUME MEASURED BY ULTRASONOGRAPHY FOR OCCULT CENTRAL LYMPH NODE METASTASIS IN PAPILLARY THYROID CARCINOMA

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Abstract—The clinical and prognostic value of tumor volume in various solid tumors has been investigated. However, there have been few studies on the clinical impact of tumor volume in papillary thyroid carcinoma (PTC). This study was performed to investigate the predictive value of estimated tumor volume measured by ultrasonography for occult central neck metastasis (OCNM) of PTC. A total of 264 patients with clinically node-negative PTC on ultrasonography and computed tomography who underwent total thyroidectomy in conjunction with at least ipsilateral prophylactic central neck dissection were enrolled in this study. Tumor volume was derived with the formula used to calculate ellipsoids from two orthogonal scans during 2-D ultrasonography at initial aspiration biopsy. We retrospectively evaluated demographic characteristics, pre-operative ultrasonographic features (tumor size, volume and multifocality) and pathologic results. The OCNM rate was 35.6%; estimated tumor volume was used to predict OCNM ($p = 0.035$). At 0.385 mL, sensitivity and specificity were 51.1% and 66.5%, and the area under the curve for OCNM detection was 0.610. In multivariate analysis, tumor volume, but not size, was an independent predictive factor for OCNM (odds ratio = 1.83, $p = 0.029$). The other factors were extrathyroidal extension (odds ratio = 2.39, $p = 0.004$) and male gender (odds ratio = 3.90, $p < 0.001$). The estimated tumor volume of PTC measured by ultrasonography could be a pre-operative predictor of OCNM. (E-mail: lsw0922@schmc.ac.kr) **© 2015 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Tumor volume, Papillary thyroid cancer, Occult central neck metastasis.**

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common form of cancer of the thyroid (Rosai 1993). In most patients, the disease follows a relatively indolent clinical course. In contrast to its excellent prognosis, PTC is associated with a high rate of metastasis to the cervical lymph nodes (>30% of patients) (Choi et al. 2008; Davidson et al. 2008; Shaha et al. 1996; Wunderbaldinger et al. 2002), correlated with recurrence in the neck. There is no consensus regarding central compartment dissection; however, recurrence exposes patients to increased morbidity because of the need for subsequent surgeries (Palme et al. 2004). The rate of central neck metastasis (CNM) has been found to increase as tumors progress in size, with extrathyroidal extension (ETE) and in locally advanced disease (Hartl and Travagli 2009).

In TNM staging, T stage is defined as the range of the primary lesion in terms of tumor size (greatest dimension) and extension to surrounding structures. Tumor cell burdens, however, are not correlated precisely with tumor stage because the greatest dimension is not completely representative of the 3-D volume (Ball et al. 2006). Several reports have addressed various methods of measuring PTC tumor volume accurately (Lyshchik et al. 2004; Romero et al. 2001). However, no pre-operative parameters for detection of occult neck metastasis are known, and there have been no reports on the clinical value of thyroid tumor volume beyond tumor size. We hypothesized that PTC tumor volume could have clinical value and may replace the size criterion. This study was performed to determine the predictive value of tumor volume as measured by ultrasonography for occult central neck metastasis (OCNM) in PTC.

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Table 1. Demographic characteristics and pre-operative data for 264 patients

Characteristic	Value	%
Age (y)	48.4 ± 11.9	
Gender (male/female)	42/222	15.9/84.1
Tumor size (mm)	10.6 ± 5.7	
BRAF mutation (positive/negative/unchecked)	156/51/57	59.1/19.3/21.6
Preoperative T stage (T1a/T1b/T2/T3/T4)	157/74/18/15/0	59.5/28.0/6.8/5.7/0

METHODS

Patients

The medical records of 634 consecutive patients who underwent thyroid surgery from March 2009 to May 2013 at SoonChunHyang University Bucheon Hospital were reviewed. Inclusion criteria were total thyroidectomy with central neck dissection, pathologically confirmed papillary thyroid carcinoma without clinically detectable cervical lymph node metastasis (cN0) and pre-operative tumor volume measured by ultrasonography. We have a policy in which at least the central lymph nodes must be removed for pathologic diagnosis and treatment. A total of 264 patients were included in our study, and we retrospectively analyzed demographic characteristics and clinical parameters, including pre-operatively measured largest diameter, volume, multifocality, $BRAF^{V600E}$ mutation and ETE. The SoonChunHyang University (Bucheon, Korea) institutional review board (SCHBC_IRB_2013-80) approved this retrospective study protocol; obtaining informed consent from patients was not deemed necessary.

Table 1 lists correlations between demographic/clinical data and thyroidectomy results in the 264 patients. Patients ranged in age from 20 to 78 y (median age = 48.4 y); 98 (37.1%) patients were <45 y of age, and 42 (15.9%) were male. Median tumor size was 10.6 ± 5.7 mm. The $BRAF^{V600E}$ mutation was detected in 156 patients (59.1%); 57 patients did not undergo pre-operative mutation screening. In 59.5% of the patients, overall pre-operative T-stage was T1a, with 28% in T1b, 6.8% in T2 and 8.5% in T3.

Volume measurements by ultrasonography

One highly experienced radiologist (H.S.H.) with 20 y of experience in thyroid imaging measured tumor volumes during the initial ultrasonographic evaluation. Ultrasound was performed with a 7- to 12-MHz linear array transducer (ATL Ultramark 9, HDI 5000, IU-22, Philips, Bothell, WA, USA). Imaging was performed at the initial diagnosis or at the time of fine-needle aspiration biopsy. Tumor volume was estimated automatically by measuring the height (H), width (W) and length (L) on two orthogonal scans (axial and sagittal) of the largest tumor, which was suspected to be malignant and confirmed as PTC by fine-needle aspiration biopsy (Fig. 1). Volume (V) was calculated with the formula used to calculate the area of an ellipsoid, $V = H \times W \times L \times 0.524$, and recorded in medical PACS (Lyshchik et al. 2004).

Statistical analysis

Receiver operating characteristic curve analysis was performed to evaluate the cutoff point of tumor volume for prediction of OCNM, and simple linear regression analysis was used for comparison with tumor size. After determination of the cutoff value, patients were divided into two groups and compared in terms of clinical data and rate of occult metastasis using the χ^2-test for categorical variables. Logistic regression analysis was used to identify the independent significance of the predictive factors. SPSS 18.0 (IBM, Armonk, NY, USA) was used for analysis of all data, and statistical significance was accepted at $p < 0.05$.

RESULTS

Table 2 summarizes measured tumor volumes and operative and pathologic data of all patents; estimated

Fig. 1. Ultrasonographic volume measurement. Tumor volume was derived automatically in two orthogonal scans with the formula used to calculate the volume of an ellipsoid: tumor volume = $A \times B \times C \times 0.524$, where A = width, B = length and C = height.