Acta Med. Okayama, 2018
Vol. 72, No. 6, pp. 577–581

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Computed Tomography Findings for Diagnosing Follicular Thyroid Neoplasms

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Since no diagnostic method has been established to distinguish follicular thyroid carcinoma (FTC) from follicular thyroid adenoma (FTA), surgery has been the only way to reach a diagnosis of follicular neoplasm. Here we investigated the computed tomography (CT) features of follicular neoplasms, toward the goal of being able to identify specific CT features allowing the preoperative differentiation of FTC from FTA. We retrospectively analyzed the cases of 205 patients who underwent preoperative CT of the neck and were histopathologically diagnosed with FTC (n = 31) or FTA (n = 174) after surgery between January 2002 and June 2016 at several hospitals in Japan. In each of these 205 cases, non-enhanced and contrast-enhanced CT images were obtained, and we analyzed the CT features. On univariate analysis, inhomogeneous features of tumor lesions on contrast-enhanced CT were more frequently observed in FTC than in FTA ($p = 0.0032$). A multivariate analysis identified inhomogeneous features of tumor lesions on contrast-enhanced CT images as an independent variable indicative of FTC ($p = 0.0023$). CT thus offers diagnostic assistance in distinguishing FTC from FTA.

Key words: computed tomography, follicular thyroid carcinoma, follicular thyroid adenoma, preoperative diagnosis

Preoperative diagnostic methods have not been established to distinguish follicular thyroid carcinoma (FTC) from follicular thyroid adenoma (FTA) [1]. Although ultrasonography (US)-guided fine needle aspiration (FNA) cytology of thyroid nodules has become the dominant modality for assessing the need for a resection of thyroid nodules, among 219 patients with preoperative FNAs reported as "suspicious for follicular neoplasm," only 19 (8.7%) were actually FTCs [2]. The rate of invasive FTCs among all follicular neoplasms is only 2% [3]. However, since the malignant potential of follicular neoplasms can rarely be determined from a cytological evaluation alone, many patients are advised to undergo surgical resection [4]. We conducted the present study to determine specific CT features for distinguishing FTCs from FTAs.

Patients and Methods

Study population. This study included 205 patients who underwent preoperative neck CT and sur-

Received February 14, 2018; accepted September 25, 2018.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

gery and were histopathologically diagnosed with FTC (n=31) or FTA (n=174) at Okayama University Hospital, Himeji Red-Cross Hospital, or National Hospital Organization Okayama Medical Center between January 2002 and June 2016. We identified these 205 cases by reviewing the medical and pathological records. All study protocols were approved by the institutional review board at each of the hospitals. The choice to perform surgery was at the discretion of the attending physician. Our fundamental policy for the treatment of thyroid nodules is to do our best to avoid unnecessary surgery, by considering the results of US-guided FNA cytology, clinical symptoms, patient age, tumor size, imaging studies, laboratory findings, or patient requests.

Neck CT. Both non-enhanced and contrast-enhanced CT images were obtained from each of the 205 patients. CT examinations were performed with CT scanners (Aquilion 64 or Aquilion One; Toshiba Medical System Corp., Tokyo). The acquisition parameters were: 120 kV; Auto Exposure Control (SD10); rotation time, 0.5 sec; pitch, 0.844 or 0.637; field of view, 24 cm; matrix size, 512×512 pixels; detector collimation, 32 mm×1.0 mm; slice thickness, 1 mm or 5 mm; and slice increment, 1 mm or 5 mm. Contrast-enhanced images were obtained after an intravenous injection of contrast medium (300 mg of non-ionized iodine per mL, 2 ml/kg) at 1 mL/sec, starting 60 sec after the initiation of contrast media.

We have noted the following 3 patterns on CT images of follicular neoplasms. Type 1: The tumor lesion is depicted as an inhomogeneous feature on contrast-enhanced images, but depicted as homogeneous on non-enhanced images (Fig. 1A). Type 2: The tumor lesion is depicted as a homogeneous feature on both non-contrast and contrast-enhanced images (Fig. 1B). Type 3: The tumor lesion is depicted as an inhomogeneous feature on non-contrast images and depicted as the same inhomogeneous feature on contrast-enhanced images (Fig. 1C).

We defined type 1 as an inhomogeneous enhanced pattern depicted on only contrast-enhanced images, and types 2 and 3 as a homogeneous enhanced pattern. In other words, we hypothesized that an irregular enhancement of nodules regardless of non-contrast CT values may suggest a malignant lesion. The type on CT images was decided by three investigators (T. Makino, Y. Orita, and T. Tachibana) who were blinded to the histopathological findings of the cases. In cases of discrepancies, a consensus was reached by discussion among these three investigators.

Statistical analysis. Uni- and multivariate logistic regression analyses were used to evaluate the predictive power of several variables to distinguish FTCs from FTAs. All analyses were performed using SPSS ver. 21.0J software (SPSS, Armonk, NY, USA). Values of $p<0.05$ were accepted as significant, and values of $p<0.1$ were considered to indicate a tendency.

Results

The mean age of the 205 patients (FTC, n=31; FTA, n=174) was 58 years (range 15-83 years). Forty-six (22%) were male and 159 (78%) were female. The mean major axis of thyroid nodules was 32 mm (range 10-77 mm). A mean value could not be calculated for the patients' serum thyroglobulin levels, because the values at one of the 3 hospitals were recorded as ≥500 ng/ml when the values were >500 ng/ml.

An inhomogeneous pattern depicted on contrast-enhanced CT was observed in 100 patients (49%). According to our definition for the CT images to discriminate between FTC and FTA, the sensitivity was 74.2%, the specificity was 55.7%, and the accuracy was 58.5%. US-guided FNA cytology was conducted in 143 FTA cases and 22 FTC cases. Among the FTA patients, 1 case was Class I, 88 cases were Class II, 52 cases were Class III, and 2 cases were Class IV. Among the FTC patients, 12 cases were Class II, and 10 cases were Class III. When we hypothesized that Class III and Class IV were "suspicious of malignant tumors," the sensitivity was 45.5%, the specificity was 62.2%, and the accuracy was 60.0%. In addition, the sensitivity, specificity and accuracy using the CT images and US-guided FNA cytology were 31.8%, 83.9% and 88.8%, respectively.

The mean duration of follow-up for the patients with FTC or FTA after their first presentation to the hospital was 12 months (range 0-154 months). Among the 31 FTC cases, 5 showed distant metastasis (synchronous, n=4; metachronous, n=1) during the observational period. Each of these 5 cases showed an inhomogeneous pattern on contrast-enhanced CT. After classifying findings from CT, only a few cases need to be discussed.

The results of the univariate analysis for these variables are shown in Table 1. Inhomogeneous tumor

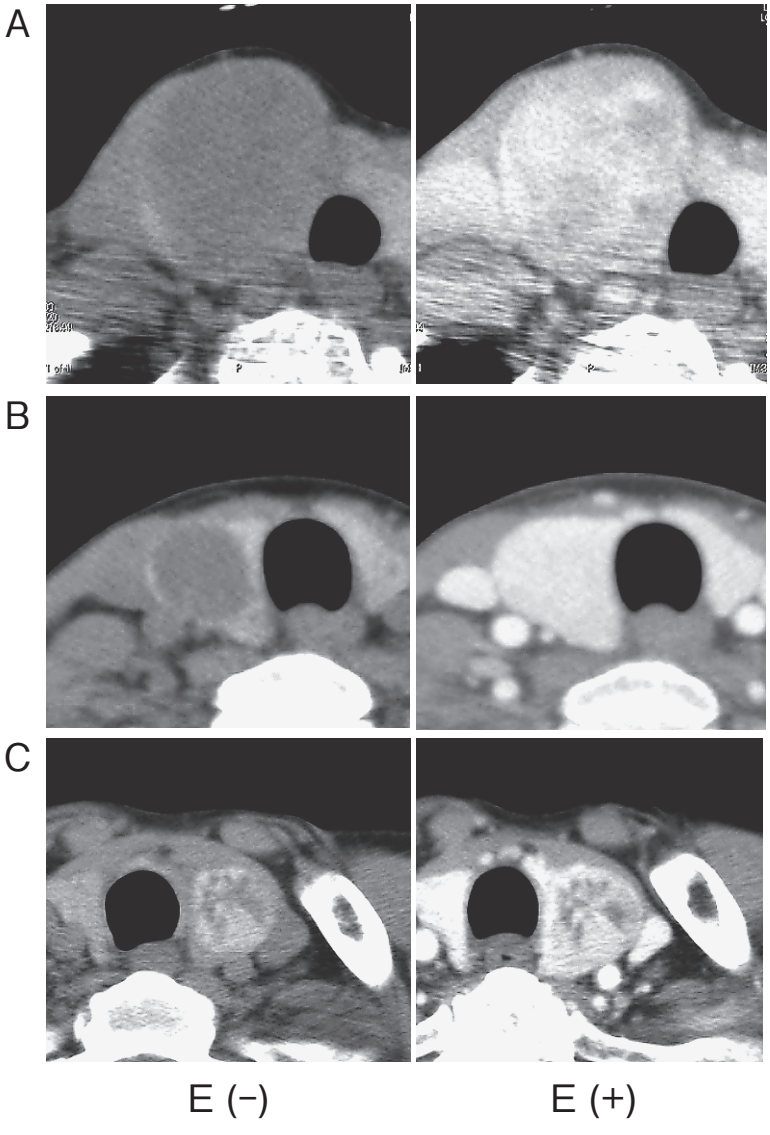

Fig. 1 **A**, Type 1, the tumor lesion is depicted as an inhomogeneous feature on contrast-enhanced images, but depicted as homogeneous on non-enhanced images; **B**, Type 2, the tumor lesion is depicted as a homogeneous feature on both non-contrast and contrast-enhanced images; **C**, Type 3, the tumor lesion is depicted as an inhomogeneous feature both on non-contrast and contrast-enhanced images.

Table 1 Univariate analysis of characteristics of the 205 patients with FTC or FTA

Characteristics	FTC (n = 31)	FTA (n = 174)	*p*-value
Age# ≥45 years (mean, 58; range, 15–83)	26 (84%)	118 (68%)	0.086
Sex, male	11 (35%)	35 (20%)	0.11
Major axis* ≥40 mm (mean, 32; range, 10–77)	14 (45%)	54 (31%)	0.19
Tg ≥300 ng/mL	11 (35%)	55 (32%)	0.57
Inhomogeneous enhanced CT pattern	23 (74%)	77 (44%)	0.0032

FTC, follicular thyroid carcinoma; FTA, follicular thyroid adenoma; Tg, serum thyroglobulin.
#Age, age at initial thyroid operation.
*Major axis, major axis of thyroid nodules.

Table 2 Multivariate analysis of characteristics for distinguishing FTCs from FTAs

Characteristics	Risk ratio	95%CI	*p*-value
Age#, ≥45 years (mean, 58; range, 15–83)	2.58	0.93–7.20	0.0701
Inhomogeneous enhanced CT pattern	3.71	1.56–8.82	0.0030

FTC, follicular thyroid carcinoma; FTA, follicular thyroid adenoma.
#Age, age at initial thyroid operation.

lesions on contrast-enhanced CT were more frequently observed in the FTC cases than in the FTA cases ($p=0.0032$). FTC tended to be more prevalent among older patients (≥45 years) than among younger patients (<45 years; $p=0.086$). The multivariate analyses to evaluate the simultaneous effects of variables for distinguishing FTCs from FTAs (Table 2) revealed inhomogeneous features of the tumor lesion on contrast-enhanced CT as an independent characteristic to indicate FTC ($p=0.0030$).

Discussion

CT often aids in the preoperative assessment of the location and extent of intrathoracic tissue and its relationship to the major vascular structures, and is used as a major radiological staging method when evaluating the extent of cervical and mediastinal adenopathy in patients with thyroid carcinoma prior to radical surgery [5]. Ultrasonography provides greater spatial resolution than CT and affords an improved evaluation of nodule architecture and consistency [6], and we usually first evaluate thyroid nodules by US. Although we almost routinely perform preoperative CT, the usefulness of CT for the diagnosis of thyroid tumor has not been investigated, and only a few attempts have been made to distinguish malignant thyroid nodules from benign nodules on CT [5-7].

Kim *et al.* [7] reported that an exophytic configuration, irregular margin, taller-than-wide shape, punctate calcifications, and homogeneously decreased enhancement were associated with a high malignancy rate. The same group [8] reported that an expansile configuration (*i.e.*, a blunt angle between the lesion and the adjacent thyroid capsule), increased enhancement, and the presence of the CT halo sign were more frequently observed in follicular neoplasms than in nodular hyperplasia. In the present study, the accuracy using the CT images was 58.5%. Jung *et al.* [9] reported that the sensitivity, specificity and accuracy of US features for follicular tumors of thyroid were 50.6%, 89.5% and 76.2%, respectively. It is clear that US is superior to CT in the diagnosis of follicular tumors, but our present analyses revealed that the inhomogeneous pattern of thyroid nodules depicted on contrast-enhanced CT offers a simple and effective method to suggest FTC, which every physician in every hospital, even non-radiologists, can easily detect. Our findings also suggest that the diagnosis of follicular neoplasm may become more accurate by combining the use of CT images and US-guided FNA cytology.

The incidence rate of FTC is higher among females than among males [9], and 20 of the 31 FTC patients (65%) in the present study were females. The gender incidence rate for FTC did not differ significantly from that for FTA. Some studies have shown that large size of a thyroid tumor is predictive of malignancy [10, 11]; however, we did not observe any significant difference in tumor size between the FTCs and FTAs. This discrepancy may be due to the fact that the patients with a major tumor axis <10 mm did not undergo surgery and thus were not included in the present study.

The preoperative serum Tg concentration was reported to be higher in follicular and Hürthle cell cancers than in benign neoplasms [12]. In the present patient series, there was no significant difference in serum Tg concentration between the FTC and FTA groups.

Several limitations must be considered when interpreting our results. First, US-guided FNA shows a relatively high false-positive rate (35%) for the preoperative detection of follicular neoplasm [13], and nodular hyperplasia cases that had been preoperatively "misdiagnosed" as follicular neoplasm when the decision regarding whether surgery would be performed were not included in this study. Prospective investigations are necessary to confirm the validity of the present findings. Second, the distinction between FTC and FTA is based on the histological demonstration of capsular or vascular invasion, but even these histological findings

are convenient diagnostic criteria for which the reliability may not be 100%. In the present study, 5 of the 31 FTC cases showed distant metastasis during the observational period. An accumulation of more "true" FTC cases that show distant metastasis is needed. Third, adapting this characteristic CT finding for the diagnosis of < 10-mm thyroid nodules (for which we usually do not perform surgery) will be difficult.

In conclusion, computed tomography offers diagnostic assistance in distinguishing follicular thyroid carcinoma from follicular thyroid adenoma. Routinely performed CT images should be more efficiently used by combining CT with the use of US or FNA cytology.

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