



Modified Transverse-Vertical Gross Examination: a Better Method for the Detection of Definite Capsular Invasion in Encapsulated Follicular-Patterned Thyroid Neoplasms

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Abstract

The diagnosis of encapsulated follicular-patterned thyroid carcinoma (EFPTC) is challenging, and the detection of capsular invasion and/or vascular invasion is essential in distinguishing benign lesions from malignant lesions. In this study, we present a modified transverse-vertical gross examination method with additional vertical cuts at the upper and lower ends of thyroid nodules. In addition, we compared the clinicopathological characteristics of patients with EFPTC between conventional and modified methods. The diagnostic rate of follicular thyroid carcinoma and invasive encapsulated follicular variant of papillary thyroid carcinoma was higher with the modified method ($p = 0.003$ and $p = 0.028$, respectively). Furthermore, the paraffin block number and the number of capsular invasion per centimeter were significantly higher with the modified method ($p < 0.001$ and $p = 0.007$, respectively). However, vascular invasion was not significantly different between the two methods ($p = 0.771$). The possibility of identifying capsular invasion was around two times higher with the modified method (odds ratio = 1.91, 95% confidence interval = 1.20–3.07, $p = 0.007$). A total of 38 samples (23%) in the modified transverse-vertical group had capsular and/or vascular invasion in the additional vertical cuts of the upper/lower ends of the tumor. Our modified transverse-vertical gross examination method was more effective than the conventional transverse examination method for the detection of capsular invasion in EFPTC. This modified gross examination method might allow a better differential diagnosis among various encapsulated micro-follicular proliferative lesions.

Keywords Follicular-patterned thyroid carcinoma · Gross examination · Capsular invasion · Vascular invasion

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Introduction

Recently, a new World Health Organization (WHO) classification of thyroid neoplasms has been proposed, and three types of follicular-patterned borderline follicular tumors were introduced including follicular tumor of uncertain malignant potential (UMP), well-differentiated tumor of UMP, and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [1]. The diagnosis of encapsulated follicular-patterned thyroid carcinoma (EFPTC) is increasingly challenging [2–4]. The detection of capsular and/or vascular invasion is essential for the histological confirmation of follicular thyroid carcinoma (FTC) and invasive encapsulated follicular variant of papillary thyroid carcinoma (FV-PTC) in diagnostic lobectomy specimens [5].

A proper gross examination is the first step for the accurate pathological diagnosis of diagnostic lobectomy specimens of the thyroid. Previous studies have indicated that evaluating the entire tumor capsule is important for the detection of capsular or vascular invasion in encapsulated follicular-patterned thyroid neoplasms (EFPTNs) [3, 6–8]. However, there is no clear recommendation on the best gross examination method to effectively evaluate the entire tumor capsule or how to obtain an adequate number of paraffin blocks from the tumor [6, 7]. Typically, the submission of at least ten horizontally sectioned blocks would likely be adequate for detecting capsular invasion in EFPTNs [3, 8, 9]. However, this might not be sufficient for the complete evaluation of the entire tumor capsule in cases of large thyroid neoplasms.

In this study, we proposed a modified transverse-vertical gross examination method, which makes additional vertical cuts at the upper and lower ends of the encapsulated thyroid nodules, and attempted to evaluate the efficacy of this modified gross examination method for the better detection of invasive foci in the entire tumor capsule of EFPTNs.

Methods

Tissue Samples and Study Design

The study protocol was approved by the Institutional Review Board of Asan Medical Center. Initially, we examined 1387 cases (624 follicular adenoma, 399 FTC, 203 non-invasive encapsulated FV-PTC/NIFTP, and 161 invasive encapsulated FV-PTC cases), which were diagnosed as EFPTN after thyroid surgery at Asan Medical Center from 2013 to 2014 by conventional transverse gross examination and from 2016 to 2017 by modified transverse-vertical gross examination (Supp. Fig. 1). To compare the number of capsular and/or vascular invasion in EFPTC without individual sampling bias between the two different gross examination methods, we confined our analyses to samples examined by a pathologist

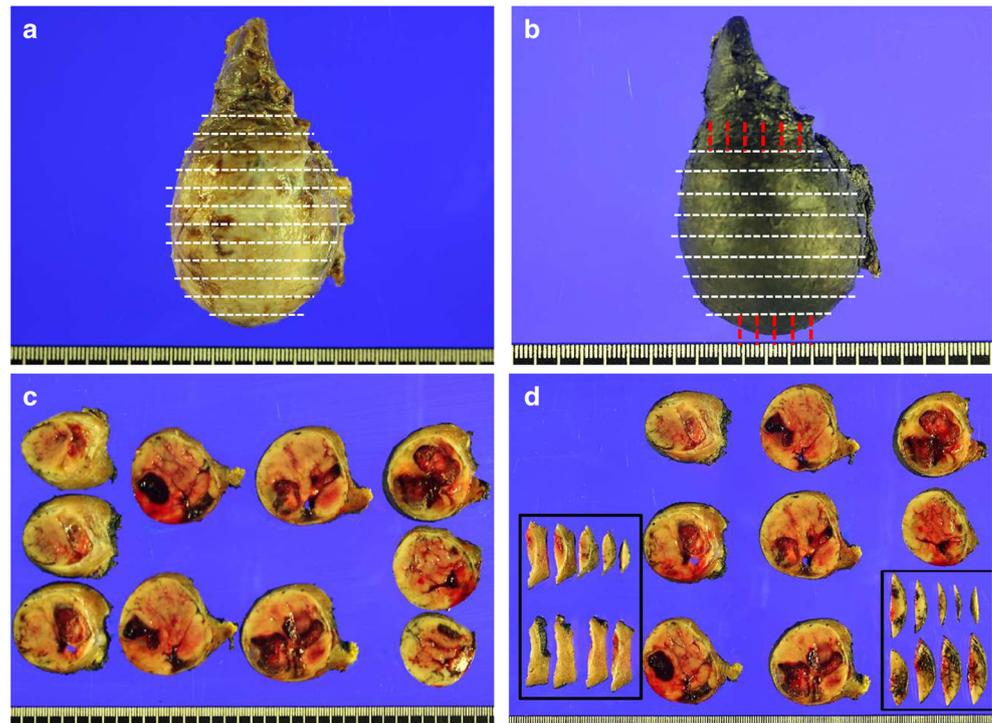
assistant (S.J.K.). Finally, we retrospectively reviewed 342 cases of minimally invasive FTC ($n = 184$), encapsulated angioinvasive FTC ($n = 39$), and invasive encapsulated FV-PTC ($n = 119$). Among 342 thyroid specimens, 177 (51.8%) samples from 2013 to 2014 were classified as the conventional transverse group, and 165 (48.2%) samples from 2016 to 2017 were classified as the modified transverse-vertical group.

The number of paraffin blocks and the number of capsular and vascular invasion per centimeter were determined by dividing their total numbers by the longest diameter of each tumor. In addition, other clinical parameters including the age at the time of diagnosis, gender, operation type, tumor diameter, N stage, bilaterality, the presence of distant metastasis, and ablation therapy with radioactive iodine were compared between the two groups.

Gross Examination

All pre-fixation and fixation procedures were similar for all cases. Tissue samples were fixed immediately after thyroid surgery in 10% neutral buffered formalin. To prevent pseudocapsular invasion at the tumor-normal interface during rigorous gross examination in the under-fixed state, all thyroid specimens were fixed over 24 h. Gross examination was mainly performed by an experienced pathologist assistant (S.J.K.) in our pathology department. In brief, the transverse section of the tumor capsule was cut at 2-mm intervals from the upper to the lower end (Fig. 1a, c) of the thyroid nodules from January 2013 to June 2014. All sections including the tumor capsule and the tumor-normal interface were submitted. We modified the gross examination method in 2015 to reduce tangential sectioning at the upper and lower ends of these nodules. For thyroid specimens from January 2016 to June 2017, an additional vertical cut was made at the 10% upper and lower ends of the thyroid nodules with the same 2-mm intervals, and the remaining tumor capsule was examined by transverse section only (Fig. 1b, d). The total surface area of the additional vertical section was around 20% of the total surface area of the tumor capsule, assuming that the tumor is completely spherical (Supp. Fig. 2A). This area of additional vertical section was not thoroughly examined and was actually overlooked when the tumor capsule was examined by transverse section only because it was embedded in the paraffin blocks except for the border. For the remaining central part of large thyroid nodules, at least one section per centimeter of the tumor diameter was submitted to exclude the possible presence of classic papillae or poorly differentiated carcinoma transformation. All tissue blocks were stained by hematoxylin and eosin (H&E).

Fig. 1 Two different gross examination methods for the encapsulated follicular-patterned carcinomas. **a, c** From 2013 to June 2014, the transverse section of the tumor capsule was cut at 2-mm intervals from the upper to the lower end of the thyroid nodules. **b, d** From January 2016 to June 2017, an additional vertical cut was made at the upper and lower ends of the thyroid nodules (**d, insets**) at the same 2-mm intervals, and the remaining tumor capsule was examined by transverse section only



Histopathological Diagnosis

All thyroid specimens were reviewed and diagnosed based on the 2017 WHO classification criteria [1] by an endocrine pathologist (D.E.S). Capsular invasions were diagnosed when tumor buds completely penetrated the outer contour of the capsule and/or when a separate satellite tumor nest with identical tumor cells was identified outside the capsule (Supp. Fig. 2B). Strict criteria was routinely applied for capsular invasion, and deeper sections (more than 3) were actively used for incomplete worrisome “Not yet” capsular invasion. If there is no definite penetration of tumor capsule on deeper sections, a diagnosis of follicular adenoma or non-invasive encapsulated FV-PTC/NIFTP was rendered instead of FT-UMP or WDT-UMP. The “Not yet” capsular invasion was not interpreted as “True” capsular invasion. Vascular invasions were diagnosed when the polypoid tumor nest was completely covered by the endothelium, attached to a wall of blood vessels within or outside the capsule, and rarely associated with a thrombus (Supp. Fig. 2C). We excluded free-floating tumor nests in vascular lumens. Vascular invasion was further classified into two groups: focal (with less than 4 vascular invasive foci) and extensive (with 4 or more invasive foci) vascular invasion [6]. The total number of capsular and vascular invasion was determined for all thyroid specimens.

Statistical Analysis

R software version 3.4.0 was used to perform statistical analyses (R Foundation for Statistical Computing, www.R-project.org). Continuous variables are presented as the mean with standard deviation or median with interquartile range (IQR), and categorical variables are presented as the frequency with percentage. The mean value was used to determine the cutoff value of the number of capsular invasion per centimeter. A binary logistic regression model was used to compare capsular invasion and vascular invasion between two methods. Values with $p < 0.05$ were considered statistically significant.

Results

Distribution of Pathologic Diagnosis of EFPTN According to Two Gross Examination Methods

Table 1 shows the distribution of pathologic diagnosis of EFPTN according to two gross examination methods. The diagnosis rate of FTC and invasive encapsulated FV-PTC was significantly increased and that of follicular adenoma and non-invasive encapsulated FV-PTC/NIFTP was decreased following the adoption of the modified transverse-vertical gross examination method (from 2016 to 2017) compared with the conventional method (from 2013 to 2014) ($p = 0.003$ and $p = 0.028$, respectively).

Table 1 Pathological diagnosis of follicular thyroid neoplasm according to two gross examination methods

	Conventional transverse	Modified transverse-vertical	<i>p</i> value
Follicular neoplasm			0.003
FA	421 (64.5%)	203 (54.9%)	
FTC	232 (35.5%)	167 (45.1%)	
EFV-PTC			0.028
Non-invasive/NIFTP	141 (60.3%)	62 (47.7%)	
Invasive	93 (39.7%)	68 (52.3%)	

FA, follicular adenoma; FTC, follicular thyroid carcinoma; EFV-PTC, encapsulated follicular variant of papillary thyroid carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features

Clinicopathological Characteristics of Patients Diagnosed with EFPTC According to Two Gross Examination Methods

The clinicopathological characteristics of 342 patients according to two gross examination methods are shown in Table 2. There was no significant difference in the age and sex between the two gross examination methods. After 2016, fewer patients underwent completion thyroidectomy following the initial surgery ($p = 0.047$). The mean tumor size was 3.2 ± 1.5 cm in the transverse group and 3.3 ± 1.5 cm in the modified transverse-vertical group ($p = 0.584$). There was no significant difference in the N stage, bilaterality, distant metastasis, and radioactive iodine ablation therapy between the two groups.

The paraffin block number per centimeter was significantly higher in the modified transverse-vertical group ($2.7 \pm 0.9/\text{cm}$) than in the transverse group ($2.3 \pm 0.9/\text{cm}$) ($p < 0.001$). The number of capsular invasion per centimeter was greater in the modified transverse-vertical group ($0.9 \pm 0.9/\text{cm}$) than in the transverse group ($0.7 \pm 0.6/\text{cm}$) ($p = 0.007$). There was no significant difference in the number of vascular invasion per centimeter and the vascular invasion patterns between the two groups ($p = 0.909$ and $p = 0.771$, respectively).

Comparison of the Detection of Capsular and Vascular Invasion by Two Gross Examination Methods

The detection of capsular or vascular invasion by the two gross examination methods was compared (Table 3). The possibility of identifying capsular invasion was around two times higher in the modified transverse-vertical group than in the conventional transverse group (odds ratio = 1.91, 95% confidence interval = 1.20–3.07, $p = 0.007$). However, there was no difference in the detection of vascular invasion between the two gross examination methods.

Patients with Capsular or Vascular Invasion at the Upper and Lower Ends of Thyroid Nodules in the Modified Transverse-Vertical Group

There were 38 cases (23%, 38/165) with capsular or vascular invasion at the upper or lower ends of thyroid nodules in the modified transverse-vertical group. In addition, 10 of the 165 cases (6.1%) revealed capsular or vascular invasion limited to the additional vertical cuts of the upper and lower ends of thyroid nodules (Table 4). In seven cases (patients 1–7), there was a single focus of capsular invasion only at the upper and lower ends of the tumor (Supp. Fig. 2B) without vascular invasion. Among them, six patients were diagnosed as FTC, and one patient was diagnosed as FV-PTC. None of the patients had lymph node or distant metastasis. In three cases (patients 8–10), there was a single focus of vascular invasion in the vertical sections at the upper and lower ends of the thyroid nodules (Supp. Fig. 2C, patient 9). All three patients were diagnosed as FTC, and one patient had distant metastasis at the initial diagnosis (patient 10). The modified gross examination method revealed extensive vascular invasion in patients 8 and 10.

Patients with Initial Distant Metastasis and Capsular Invasion Only

Three patients (0.9%, 3/342) had synchronous distant metastasis and capsular invasion only. The clinicopathological features of these patients are shown in Supp. Table 1. All of them had initial distant metastasis; however, vascular invasion was not detected in the thyroid specimens. Two of them (1.1%, 2/177) were evaluated by the transverse gross examination method, and only a single focus of capsular invasion was detected for each of them. One of them (0.6%, 1/165) was evaluated by the modified transverse-vertical gross examination method, which revealed up to five foci of capsular invasion.

Discussion

The identification of capsular or vascular invasion is essential for the histological confirmation of EFPTC and the exclusion of NIFTP [3, 5]. We proposed an effective modified gross examination method, which demonstrated a better prediction of malignancy in EFPTNs. In the analysis of EFPTC specimens, capsular invasion was more frequently detected using the modified transverse-vertical method compared with the conventional transverse method. The possibility of identifying capsular invasion was around two times higher in the modified transverse-vertical group than in the conventional transverse group.

Table 2 Clinicopathological characteristics of encapsulated follicular thyroid carcinoma according to two gross examination methods

	Conventional transverse (n = 177)	Modified transverse-vertical (n = 165)	p value
Age	49.9 ± 14.1	47.4 ± 13.1	0.084
Sex (female)	128 (72.3%)	116 (70.3%)	0.770
Operation type			0.047
Lobectomy	111 (62.7%)	121 (73.3%)	
Total thyroidectomy	66 (37.3%)	44 (24.7%)	
Tumor diameter (cm)	3.2 ± 1.5	3.3 ± 1.5	0.584
N stage			0.625
N1a	3 (1.7%)	3 (1.8%)	
N1b	1 (0.6%)	0 (0.0%)	
Bilateral tumor	3 (1.7%)	3 (1.8%)	0.999
Distant metastasis			0.380
Lung	1 (0.6%)	2 (1.2%)	
Bone	4 (2.3%)	1 (0.6%)	
Lung and bone	0 (0.0%)	1 (0.6%)	
RAI therapy	61 (34.5%)	42 (25.5%)	0.090
Block number/cm	2.3 ± 0.9	2.7 ± 0.9	< 0.001
Capsular invasion/cm	0.7 ± 0.6	0.9 ± 0.9	0.007
Capsular invasion/cm			0.002
0–0.8	130 (73.4%)	94 (57.0%)	
≥ 0.8	47 (26.6%)	71 (43.0%)	
Vascular invasion/cm	0.4 ± 1.0	0.4 ± 1.2	0.909
Vascular invasion			0.771
No	147 (83.1%)	139 (84.2%)	
Focal (less than 4 foci)	26 (14.7%)	20 (12.1%)	
Extensive (4 or more foci)	4 (2.3%)	6 (3.6%)	

RAI, radioactive iodine

In the new WHO classification system, the concept of borderline tumors with UMP was adopted, and follicular carcinoma was categorized into three subgroups [1, 10]. To differentiate malignant tumors from borderline tumors, the accurate

Table 3 Comparison of the detection of capsular and vascular invasion by two gross examination methods

	OR	95% CI	p value
Capsular invasion			
Unadjusted	2.09	1.33–3.30	0.001
After adjustment*	1.91	1.20–3.07	0.007
Vascular invasion			
Unadjusted	0.92	0.51–1.63	0.766
After adjustment*	1.05	0.57–1.92	0.882

*Adjusted for age, sex, pathological diagnosis, and surgical extent

OR, odds ratio; CI, confidence interval

assessment of capsular invasion and/or vascular invasion is important. Moreover, the effective gross examination of the entire tumor capsule is an essential first step because of the lack of specific molecular markers for predicting malignancy in EFPTNs, and diagnostic lobectomy is currently the best approach for histological confirmation [5].

An evaluation of the entire thyroid capsule including the tumor and the adjacent surrounding thyroid parenchyma is ideal for the detection of capsular or vascular invasion in EFPTNs [3, 5–8]. According to Yamashina, an extensive circumferential dissection of the entire capsule in follicular neoplasms is the ideal gross examination method to avoid tangential sectioning completely [11]. However, Yamashina's approach has some practical difficulty in obtaining regular thin sections and embedding in paraffin blocks because of the irregular thickness of the sections. A guideline from the Japanese Society of Thyroid Surgery and Kakudo et al. suggested a gross method for examining EFPTNs, which is similar to our method by adding perpendicular cuts to the peripheral slices after making multiple sagittal cuts [12]. However, there is no clear recommendation on how to evaluate effectively the entire tumor capsule or how much is an adequate number of paraffin blocks from these tumors [6, 7]. Several studies have proposed that the submission of at least ten horizontally sectioned blocks with 2–3 sections in each block would likely to be adequate for detecting capsular invasion in EFPTNs [3, 8, 9]. In our modified transverse-vertical method, the additional vertical sections were rendered at the 10% upper and lower ends of the thyroid nodules to examine the entire tumor capsule equally and extensively. We found that these vertical sections accounted for up to 20% of the entire capsular surface area. There might be a risk of under-diagnosis for 4.2% (7/165) of patients, who had only single focus of capsular invasion in the vertical sections of the upper or lower ends of thyroid nodules. If these patients were examined with the conventional transverse method, they might have been misdiagnosed as having benign tumors although the therapeutic plan would not have been different [13]. In addition, the modified method revealed extensive vascular invasion in two patients, and they had a single focus of vascular invasion in the vertical sections of the upper or lower ends of thyroid nodules. The vertical sections effectively demonstrated perpendicular capsular invasion and rare vascular invasion at the tumor-normal interface with the same alignment at the upper or lower ends of thyroid nodules with different diameters.

Previous studies have reported that the sampling number or the extent of gross examination (complete versus incomplete) could be significantly associated with metastatic progression of FTC [14, 15]. This indicated that the first step of histological evaluation (gross examination) might affect both accurate pathological diagnosis and the prediction of the clinical outcomes of patients. However, there is another study that reported no association between tumor sampling and clinical

Table 4 Clinicopathological features of patients with capsular or vascular invasion at the vertical sections of the upper/lower ends of thyroid nodules in the modified transverse-vertical group

Patient	Age/ sex	Pathology	Size (cm)	Capsular inv.	Vascular inv. (vertical section)	LNM	Distant metastasis
1	47/F	FTC	2.6	1	0	0	0
2	44/F	FTC	2.0	1	0	0	0
3	36/F	FTC	2.8	1	0	0	0
4	56/F	FV-PTC	2.0	1	0	0	0
5	44/M	FTC	2.2	1	0	0	0
6	32/M	FTC	3.2	1	0	0	0
7	21/F	FTC	4.5	1	0	0	0
8	48/F	FTC	2.7	10	4 (1)	0	0
9	28/F	FTC	2.3	1	1 (1)	0	0
10	65/M	FTC	3.2	4	4 (1)	0	1

F, female; *M*, male; *Inv.*, invasion; *LNM*, lymph node metastasis; *FTC*, follicular thyroid carcinoma; *FV-PTC*, encapsulated follicular variant of papillary thyroid carcinoma

outcome of the FTC patients [16]. Despite the limited clinical impact, this modified transverse-vertical gross examination method increased the diagnostic rate of FTC and invasive encapsulated FV-PTC by increased detection of definite capsular invasion in EFPTNs.

The number of vascular invasion is important in patients with FTC because it may be directly associated with the clinical outcomes of patients [17–21]. Vascular invasion is considered as an independent risk factor for distant metastasis in FTC [17–19, 22]. However, in some cases of minimally invasive FTC without vascular invasion, there may be synchronous distant metastasis [8, 23, 24]. In the present study, three patients (0.9%) had synchronous distant metastasis without vascular invasion. Two of them had only a single focus of capsular invasion by the conventional transverse method, and they might have been under-diagnosed as having follicular adenoma with the conventional transverse method if the tumor capsule had been submitted incompletely.

There are some limitations in the present study. First, it is a single-center and retrospective study; thus, there may be a selection bias. Second, we could not evaluate clinical outcomes with the two different gross examination methods due to the relatively short follow-up duration. Third, we did not evaluate the inter-observer and intra-observer variation in the pathological diagnosis of these thyroid nodules. Furthermore, sampling error cannot be entirely eliminated because only a limited thickness of each paraffin block was confirmed by an endocrine pathologist.

In this study, by adding vertical sections to the upper and lower ends of tumor capsule, we revealed the presence of definite capsular invasion in these areas and suggested this method as an effective even sampling method of the entire tumor capsule. Despite the limited clinical impact, this modified transverse-vertical gross examination method increased the diagnostic rate of FTC and invasive encapsulated FV-PTC by increased detection of definite capsular invasion in EFPTNs.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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