



# The Intraoperative Immunohistochemical Staining of CD56 and CK19 Improves Surgical Decision for Thyroid Follicular Lesions

Ju Yeon Pyo · Sung-eun Choi  
Eunah Shin<sup>1</sup> · JaSeung Koo<sup>2</sup>  
SoonWon Hong

Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; <sup>1</sup>Department of Pathology, CHA Gangnam Medical Center, CHA University, Seoul; <sup>2</sup>Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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## Corresponding Author

SoonWon Hong, MD, PhD  
Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea  
Tel: +82-2-2019-3540  
Fax: +82-2-3463-2103  
E-mail: soonwonh@yuhs.ac

**Background:** When differential diagnosis is difficult in thyroid follicular lesions with overlapping histological features, the immunohistochemical staining can help confirm the diagnosis. We aimed to evaluate the effectiveness of rapid immunohistochemical stains of CD56 and cytokeratin 19 on frozen sections of thyroid follicular lesion and explore the possible gains and limitations of the practice. **Methods:** Eighty-six nodules of 79 patients whose intraoperative frozen sections were selected as the control group, and 53 nodules of 48 patients whose intraoperative frozen sections were subject to rapid immunohistochemistry were selected as the study group. **Results:** Five nodules (6%) in the control group were diagnosed as follicular neoplasm and six nodules (7%) were deferred. In the study group, six nodules (11%) were follicular neoplasm and none were deferred. Three nodules (4%) in the control group showed diagnostic discrepancy between the frozen and permanent diagnoses, but none in the study group. The average turnaround time for the frozen diagnosis of the control group was 24 minutes, whereas it was 54 minutes for the study group. **Conclusions:** Intraoperative rapid immunohistochemical stains significantly decreased the diagnostic discrepancy in this study. Considering the adverse effects of indefinite frozen diagnosis or discrepancy with permanent diagnoses, the intraoperative rapid immunohistochemical stain can help to accurately diagnose and hence provide guidance to surgical treatment.

**Key Words:** Thyroid; Follicular patterned lesion; Immunohistochemistry; Frozen; CD56; CK19

Follicular patterned lesions of the thyroid impose not so trivial diagnostic difficulty because the cytological features can be deceiving and the diagnosis of malignancy depends on non-disputable histologic evidence other than morphologic criteria.<sup>1</sup> Thus, unlike other tumors, a limited number of representative sections of the lesion cannot be relied upon for an accurate diagnosis, and the diagnostic accuracy of fine needle aspiration and intraoperative frozen diagnosis are often compromised.<sup>2</sup> Moreover, it is not surprising to find that even thyroid experts have discrepancy in the diagnosis of follicular lesions, harboring the entire spectrum of benign to malignant tumors,<sup>3-6</sup> and yet, an accurate diagnosis is just as important for the follicular patterned lesions as for other tumors because treatment plans totally depend on the pathologic diagnosis. As such, there have been efforts to more actively utilize core biopsy in the diagnosis of thyroid lesions with expectations that immunohistochemical (IHC) stains will aid in more accurate diagnosis.<sup>7-9</sup> However, we must not overlook the fact that IHC stains in follicular patterned lesions can vary from area to area,<sup>10</sup>

and so the IHC stain results in the core biopsy can be more often misleading than not. We also should consider the fact that for follicular neoplasm, a key to the diagnosis is the presence or absence of a complete capsule of the entire lesion,<sup>1</sup> which can never be accurately assessed by core biopsy alone, irrespective of the IHC stain results. These limitations in the preoperative diagnosis of the follicular patterned lesions naturally lead to the conclusion that at present, there is no alternative other than assessing the histology of the entire lesion in cases of follicular patterned lesions. However, we propose that if not preoperatively, we can at least aid in making surgical decision intraoperatively by applying IHC stain to frozen section. Even though differential diagnosis of the follicular neoplasm and follicular variant papillary thyroid carcinoma (FVPTC) is difficult on frozen sections, shedding light on the more possible diagnosis between the two is plausible by frozen section and it can be an aid enough for the surgeon. We propose that IHC stains that are ancillary in the differential diagnosis of follicular neoplasm and FVPTC can also be applied

to the frozen section intraoperatively, and among many that are used in permanent sections, we chose CD56 and cytokeratin 19 (CK19) based on our past experiences. We aimed to evaluate the exact positive yields of the IHC stains on intraoperative frozen sections and explore the possible gains and limitations of the practice.

## MATERIALS AND METHODS

### Patients and nodules

Eighty-six nodules of 79 patients whose intraoperative frozen sections were not subject to IHC stains at all were selected as the control group (Fig. 1A) and 53 nodules of 48 patients whose intraoperative frozen sections could be subject to IHC stains if necessary were selected as the study group (Fig. 1B). For each group, the study duration was about a month. This study was approved by the Institutional Review Board of Gangnam Severance Hospital with a waiver of informed consent (IRB No. 3-2015-0133).

### Rapid IHC stain

Fresh frozen tissue in OCT compound was sectioned with Cryo-cut Microtome (Leica Biosystems, Newcastle Upon Tyne, UK) in 3–4  $\mu\text{m}$  thickness, placed on silane coated slide, and let dry. The slide was then stained for rapid immunohistochemistry in LEICA BOND-III Autostainer using Bond Polymer Refine Detection kit (Leica Biosystems). Briefly, the dry slide was fixed in 4% paraformaldehyde for 1 minute, immersed in peroxide block for 2 minutes to endogenous peroxidase blocking, washed and then applied with primary antibody for 4 minutes. After washing with Bond Wash solution, the slide was sequentially applied with post primary agent for 2 minutes and polymer for 2 minutes with washings in-between. The antibodies used were CK19 (1:80, RCK108, mouse monoclonal, DAKO, Carpinteria, CA, USA) and CD56 (1:50, 123C3, mouse monoclonal, DAKO). They were detected with 3,3'-diaminobenzidine (DAB) chromogen and DAB enhancer and counterstained with hematoxylin. The entire process takes roughly about 30 minutes.

### Microscopic evaluation

Nodules of the control group were intraoperatively diagnosed based on the hematoxylin and eosin (H&E) findings alone and the total amount of time spent on the diagnosis, so-called turnaround time, was recorded. Nodules of the study group were subject to IHC stains for CD56 and CK19 only when the diagnosis could not be reached on H&E findings alone. When H&E findings were informative enough for definitive diagnosis, IHC stains

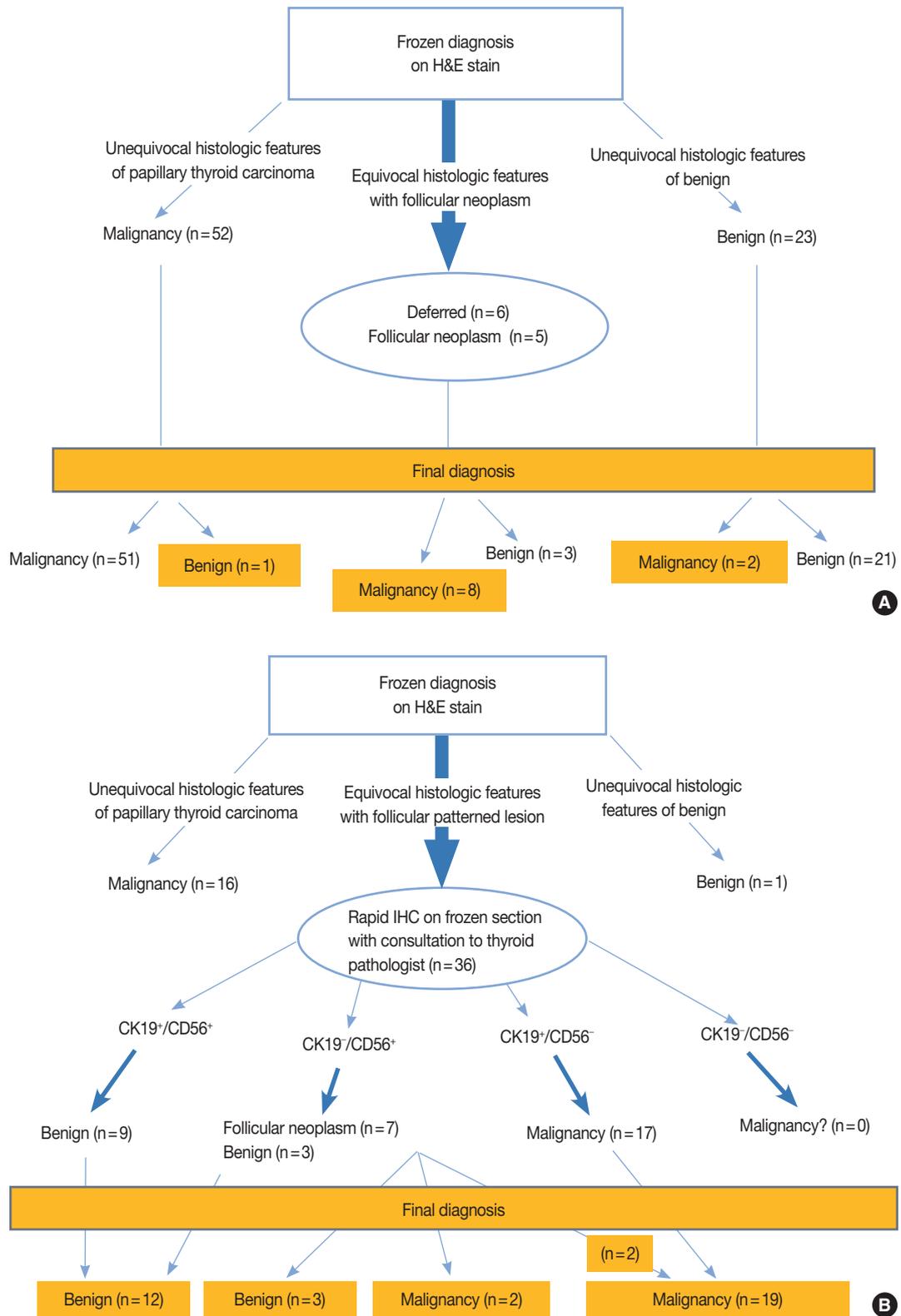
were not performed and the turnaround time was recorded. According to El Demellawy *et al.*,<sup>11</sup> membranous staining of follicular epithelial cells for CD56 ( $\geq 10\%$  cut-off) was considered positive. As shown in the diagnostic algorithm of Fig. 1B, those lesions showing cytological features suspicious for, but not diagnostic of, papillary thyroid carcinoma (PTC) were subject to IHC stains, and PTC was diagnosed when the suspicious cells were CD56-negative and CK19-positive (Fig. 2A–C). When the suspicious cells were CD56-positive, however, the diagnosis of either follicular neoplasm (Fig. 2D–F) or adenomatous hyperplasia (Fig. 2G–I) was reached.<sup>11–13</sup> These diagnoses were based upon consultation to an experienced thyroid pathologist (S.W. Hong). The turnaround time was recorded after the IHC stains for the study group. For the control group, the frozen diagnoses were deferred when the histological or cytological features of the nodules were equivocal or when the histological features were suspicious of follicular neoplasm (Fig. 1A). The intraoperative diagnoses were classified as benign, malignant, follicular neoplasm, and deferred. The number of lesions showing discrepancy between the frozen diagnosis and permanent diagnosis and the type of discrepancy were evaluated in those that were not deferred in the intraoperative diagnosis. Final diagnoses on the permanent sections of the deferred lesions and those that were reported as follicular neoplasm intraoperatively were also evaluated.

### Statistical analysis

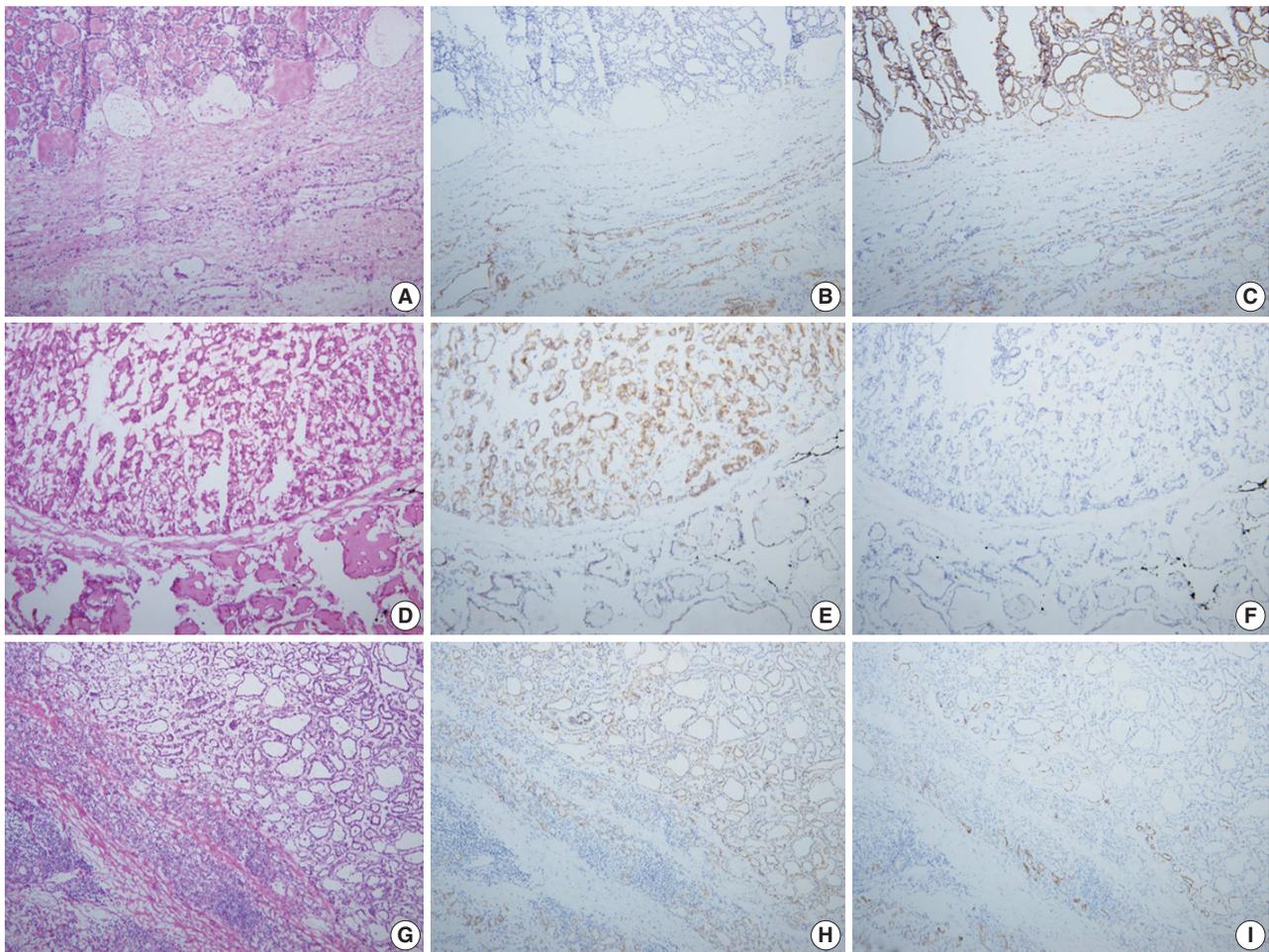
The type of intraoperative diagnosis, the number of discrepancy between the frozen diagnosis and the final permanent diagnosis, and the turnaround time in the intraoperative diagnosis of the two groups were analyzed by Student's *t* test and Fisher exact test. Statistical analysis of data was performed using the SPSS software ver. 17.0 (SPSS Inc., Chicago, IL, USA). The *p*-value less than .05 were considered statistically significant.

## RESULTS

Seventy-nine patients allocated to the control group consisted of 14 men and 65 women. Forty-eight patients in the study group consisted of eight men and 40 women. The clinicopathologic characteristics in two groups were tabulated (Table 1). There was no significant statistical difference in the distribution of gender and age between the two groups. A total of 84 nodules out of 86 in the control group (98%) were diagnosed within 40 minutes and only two nodules (2%) were diagnosed after 40 minutes. The turnaround time of 40 minutes was agreed to be a reasonable cutoff by the departments of pathology and surgery, considering



**Fig. 1.** Diagnostic algorithm of thyroid follicular patterned lesions on frozen section. (A) Control group. (B) Study group. H&E, hematoxylin and eosin; IHC, immunohistochemistry; CK19, cytokeratin 19.



**Fig. 2.** Histologic and immunohistochemical features of thyroid follicular lesions. (A) Frozen section of follicular patterned lesion reported as follicular variant papillary carcinoma. (B) Immunohistochemical stain for CD56 showing diffuse negative reaction in the tumor cells as opposed to the adjacent normal thyroid tissue. (C) Immunohistochemical stain for cytokeratin 19 (CK19) showing diffuse strong positive reaction in the tumor cells. (D) Frozen section of follicular patterned lesion reported as follicular neoplasm. (E) Immunohistochemical stain for CD56 showing diffuse positive reaction in the tumor cells as opposed to the adjacent normal thyroid tissue. (F) Immunohistochemical stain for CK19 showing diffuse negative reaction. (G) Frozen section of follicular patterned lesion reported as adenomatous hyperplasia. (H) Immunohistochemical stain for CD56 showing multifocal patchy positive reaction in the tumor cells and the adjacent normal thyroid tissue as well. (I) Immunohistochemical stain for CK19 showing positive reaction in the adjacent normal thyroid and also in a few tumor cells though much attenuated.

the time required to construct one block of typical frozen section and the time required for rapid IHC. This is in line with the guidelines recommended by the Joint Commission of International Certification and the guidelines for quality management of the Korean Society of Pathologists. For frozen sections without immunostaining, the turnaround time was kept within 15 minutes to 20 minutes. The average turnaround time to diagnosis was 24 minutes for the control group. For the study group, 17 out of 53 nodules (32%) were diagnosed within 40 minutes and 36 nodules (68%) were diagnosed after 40 minutes ( $p < .000$ ). The average turnaround time for the study group was 57 minutes (Table 1). As for the type of intraoperative frozen diagnosis, in

75 out of 86 nodules of the control group (87%) and 47 out of 53 nodules of the study group (89%), a clear definite diagnosis was possible. Five out of 86 nodules in the control group (6%) were diagnosed as follicular neoplasm, and six nodules (7%) were deferred. In contrast, six nodules out of 53 in the study group (11%) were diagnosed as follicular neoplasm, and none were deferred. There was no significant statistical difference in the distribution of intraoperative frozen diagnosis between the two groups (Table 1).

With respect to the diagnostic discrepancy between frozen diagnosis and permanent diagnosis in the two groups, three nodules out of 75 (4%) in the control group showed discrepancy

**Table 1.** Clinicopathologic features of the control group and the study group

Parameter	Control group	Study group	p-value
Sex (man:woman) <sup>a</sup>	14:65 (18:82)	8:40 (17:83)	1.000 <sup>b</sup>
Age, mean (range, yr) <sup>a</sup>	49 (24–75)	45 (24–68)	.258 <sup>c</sup>
Man	50 (32–75)	54 (41–68)	
Woman	47 (24–70)	44 (24–64)	
Turnaround time (min) <sup>d</sup>			
Mean	24	57	.000 <sup>b</sup>
<40 min	84 (98)	17 (32)	
≥40 min	2 (2)	36 (68)	
Frozen diagnosis <sup>d</sup>			.149 <sup>b</sup>
Benign	23 (27)	12 (23)	
AH	20 (23)	8 (15)	
LT	3 (4)	4 (7)	
Malignancy	52 (60)	35 (66)	
PTC, conventional	43 (50)	29 (55)	
FVPTC	7 (8)	4 (7)	
PTC, oncocytic variant	1 (1)	0	
HC	0	1 (2)	
FC	1 (1)	1 (2)	
Follicular neoplasm	5 (6)	6 (11)	
Deferred	6 (7)	0	

Values are presented as number (%), unless otherwise indicated.

AH, adenomatous hyperplasia; LT, lymphocytic thyroiditis; PTC, papillary thyroid carcinoma; FVPTC, follicular variant papillary thyroid carcinoma; HC, Hurthle cell carcinoma; FC, follicular carcinoma, minimally invasive.

<sup>a</sup>Number of patients: control (n = 79), study group (n = 48); <sup>b</sup>Fisher exact test; <sup>c</sup>t test; <sup>d</sup>Number of nodules: control (n = 86), study group (n = 53).

in the diagnosis; two cases were initially diagnosed as adenomatous hyperplasia and lymphocytic thyroiditis on frozen sections, and then as conventional PTC and noninvasive capsulated FVPTC on permanent sections (discrepancy rate, 0.087); and one nodule was initially diagnosed as conventional PTC on frozen section, and then as lymphocytic thyroiditis on permanent section (discrepancy rate, 0.019). None of the study group had discrepancy between the frozen and permanent diagnoses (discrepancy rate, 0). Although they are not classified as a discrepancy, six malignant nodules in the control group turned out to be different histologic types in permanent sections (Table 2). In the control group, two out of five follicular neoplasms on frozen section turned out to be FVPTC on permanent sections. In the study group, two out of six follicular neoplasms on frozen section were diagnosed as oncocytic variant PTC and noninvasive capsulated FVPTC on permanent sections, due to different nuclear features and IHC profiles on permanent sections (Table 3). Four out of six deferred nodules of the control group were revealed to be FVPTC on permanent diagnosis (malignancy rate, 0.667) (Table 4). Immunophenotypes of 36 nodules in the study group are summarized in Table 5. All of nine nodules (CK19<sup>+</sup>, CD56<sup>+</sup>) were immunohistochemically matched with benign on permanent diagnosis, and all of 15 nodules (CK19<sup>+</sup>, CD56<sup>-</sup>) were matched with conventional PTC. Two nodules which were initially diagnosed as follicular neoplasm due to the

**Table 2.** Diagnostic discrepancy between frozen and permanent diagnoses in each group

Frozen diagnosis (No. of nodules)	Permanent diagnosis (No. of nodules)							Discrepancy rate	
	Benign		Malignant						
	AH	LT	PTCc	FVPTC cap+, inv-	FVPTC cap+, inv+	FVPTC cap-	HC		FC
<b>Control group</b>									
Benign (n = 23)									0.087
AH	19	0	1	0	0	0	0	0	
LT	0	2	0	1	0	0	0	0	
Malignant (n = 52)									0.019
PTCc	0	1	38	0	1	2	1	0	
FVPTC	0	0	0	0	0	6	0	1	
HC	0	0	0	0	0	0	0	0	
FC	0	0	0	1	0	0	0	0	
<b>Study group</b>									
Benign (n = 12)									0
AH	8	0	0	0	0	0	0	0	
LT	0	4	0	0	0	0	0	0	
Malignant (n = 35)									0
PTCc	0	0	29	0	0	0	0	0	
FVPTC	0	0	0	1	3	0	0	0	
HC	0	0	0	0	0	0	1	0	
FC	0	0	0	0	0	0	0	1	

AH, adenomatous hyperplasia; LT, lymphocytic thyroiditis; PTCc, papillary thyroid carcinoma, conventional; FVPTC, follicular variant papillary thyroid carcinoma; cap+, capsule present; inv-, no capsule invasion; inv+, capsule invasion present; cap-, no capsule; HC, Hurthle cell carcinoma; FC, follicular carcinoma, minimally invasive.

IHC staining results of CK19<sup>-</sup> and CD56<sup>+</sup> were finally diagnosed as oncocytic variant PTC in one and FVPTC in the other; the IHC stain results were reversed to CK19<sup>+</sup> and CD56<sup>-</sup> on permanent sections.

## DISCUSSION

Application of IHC to frozen sections can diminish critical diagnostic discrepancy between the intraoperative frozen diagnosis and subsequent permanent diagnosis. In our study, those that were not subject to IHC on frozen sections showed a diagnostic discrepancy in 4%, a change in histologic subtype of malignant nodules in 11%, and a diagnostic deferral in 7%. In those with a

diagnostic discrepancy, for example, FVPTC was misdiagnosed as lymphocytic thyroiditis intraoperatively, lymphocytic thyroiditis was mistaken for conventional PTC, and conventional PTC was missed due to a sampling error. In addition, six out of 52 malignant nodules in the control group showed altered histological subtypes, but there was no difference in the 35 malignant nodules of the study group. Most of the deferred lesions and lesions of follicular neoplasm were finally diagnosed as capsulated FVPTC. However, those to which IHC was applied intraoperatively did not have any diagnostic discrepancy and none of them were deferred.

With the introduction of FVPTC in 1977,<sup>14</sup> many cases previously thought to be follicular neoplasm were confirmed to be, in fact, FVPTC. This has led to a rather increased frequency of intra-

**Table 3.** Malignancy rate of FN between frozen and permanent diagnoses in each group

FN at frozen diagnosis (No. of nodules)	Permanent diagnosis (No. of nodules)										Malignancy rate
	Follicular neoplasm					Other					
	Benign		Malignant			Total	AH	PTCo	FVPTC cap+, inv-	FVPTC cap+, inv+	
FA	HA	HC	FC								
Control group (n=5)	1	0	1	1	3 (60)	0	0	1	1	2 (40)	0.800
Study group (n=6)	2	1	0	0	3 (50)	1	1 <sup>a</sup>	1 <sup>a</sup>	0	3 (50)	0.333

Values are presented as number (%).

FN, follicular neoplasm; FA, follicular adenoma; HA, hurthle cell adenoma; HC, hurthle cell carcinoma; FC, follicular carcinoma, minimally invasive; AH, adenomatous hyperplasia; PTCo, oncocytic variant of papillary thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma; cap+, tumor capsule present; inv-, no capsule invasion; inv+, capsule invasion present.

<sup>a</sup>Although it showed CD56 positivity and cytokeratin 19 (CK19) negativity on rapid immunohistochemical stain of frozen section, focal loss of CD56 and focal reactivity of CK19 were revealed on permanent section of remained lesion.

**Table 4.** Malignancy rate of deferred lesion between frozen and permanent diagnoses in each group

Frozen diagnosis (deferred)	Permanent diagnosis (No. of nodules)								Malignancy rate
	Benign (n=2)				Malignant (n=4)				
	FA	HA	AH	PTCo	FVPTC cap+, inv-	FVPTC cap+, inv+	HC	FC	
Control group	1	0	1	0	4	0	0	0	0.667
Study group	0	0	0	0	0	0	0	0	0

FA, follicular adenoma; HA, hurthle cell adenoma; AH, adenomatous hyperplasia; PTCo, oncocytic variant of papillary thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma; cap+, tumor capsule present; inv-, no capsule invasion; inv+, capsule invasion present; HC, hurthle cell carcinoma; FC, follicular carcinoma, minimally invasive.

**Table 5.** Immunophenotypes of the study group nodules that were subject to rapid immunohistochemical stain

Immunophenotype	Permanent diagnosis (No. of nodules)									Total No. of nodules (n = 36)
	Benign (n = 15)				Malignant (n = 21)					
	AH	LT	FA	HA	FC	HC	PTCc	PTCo	FVPTC	
CK19 <sup>+</sup> /CD56 <sup>+</sup>	6	3	0	0	0	0	0	0	0	9
CK19 <sup>-</sup> /CD56 <sup>+</sup>	3	0	2	1	1	1	0	0	0	8
CK19 <sup>+</sup> /CD56 <sup>-</sup>	0	0	0	0	0	0	15	1 <sup>a</sup>	3 <sup>a</sup>	19
CK19 <sup>-</sup> /CD56 <sup>-</sup>	0	0	0	0	0	0	0	0	0	0

AH, adenomatous hyperplasia; LT, lymphocytic thyroiditis; FA, follicular adenoma; HA, hurthle cell adenoma; FC, follicular carcinoma, minimally invasive; HC, hurthle cell carcinoma; PTCc, papillary thyroid carcinoma, conventional; PTCo, oncocytic variant of papillary thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma.

<sup>a</sup>Although it showed CD56 positivity and cytokeratin 19 (CK19) negativity on rapid immunohistochemical stain of frozen section, focal loss of CD56 and focal reactivity of CK19 were revealed on permanent section of remained lesion.

operative pathologic consultation by frozen section in cases that had been preoperatively diagnosed as follicular neoplasm or reported to have some degree of nuclear atypia. Of course, these cases cannot be definitively diagnosed on frozen sections and they require meticulous sampling and ancillary IHC stain on permanent sections to reach definitive diagnosis.<sup>11-13</sup> To our knowledge, there has not yet been any report in thyroid lesions that employed the use of IHC in the intraoperative frozen diagnosis. Follicular neoplasm, by definition, cannot be a candidate for frozen diagnosis because its diagnosis depends on the histologic examination of the entire capsule of the mass.<sup>15</sup> However, as FVPTC has entered the diagnostic spectrum, a possible follicular neoplasm has also become a candidate for frozen diagnosis in order to rule out the possibility of FVPTC<sup>16</sup> which, in contrast to the follicular neoplasm, can be diagnosed on representative sections of the mass like other PTCs. At this point, we should note that considering the morphologic and gross features of FVPTC, there is always a hindrance of misinterpreting the microscopic appearance on frozen sections due to frozen artifacts.<sup>17</sup> In our institution, we have an experience of detecting micrometastasis in lymph nodes of breast cancer patients by applying IHC stain for cytokeratin on frozen sections.<sup>18</sup> With this previous experience, we applied IHC on frozen sections of the thyroid follicular lesions, expecting to distinguish between malignant and benign lesions intraoperatively and hence minimize the number of deferred or misdiagnosed lesions.

Many antibodies are now being used in the diagnosis of FVPTC,<sup>11-13</sup> but we chose CD56 and CK19 based on the integrated results of many antibodies and our accumulated experience heretofore. The combined results of CD56 negativity and CK19 positivity can maximize the diagnosis of PTC. Moreover, in contrast to HBME1, CK19 is often positive not only in PTC but also in adenomatous hyperplasia as well,<sup>11-13</sup> and this has led us to integrate the staining patterns of the two antibodies in the differential diagnosis of follicular patterned lesions. In our study, we could definitely diagnose PTC and FVPTC in follicular patterned lesions showing atypical nuclear features with a constant IHC staining pattern of CK19<sup>+</sup> and CD56<sup>-</sup>. On the other hand, we could avoid overdiagnosis by confirming an IHC staining pattern of CK19<sup>+</sup> and CD56<sup>+</sup> in benign follicular lesions such as lymphocytic thyroiditis, even with nuclear atypia.

The study group showed a longer turnaround time, which was 33 minutes longer than that of the control group in average, and 68% of them took more than 40 minutes in the diagnosis. However, we should consider the total cost and psychological trauma of patients in the control group whose diagnoses were deferred

(7%) or discrepant (4%). The time taken in IHC staining can be shortened to some extent although limited, but we expect to shorten the turnaround time more effectively if only we can decide with more speed whether the case in hand needs IHC on frozen section or not.

Most of the nodules diagnosed as follicular neoplasm were finally diagnosed as FVPTC. Four out of five nodules of the control group were diagnosed as follicular carcinoma in one, hurthle cell carcinoma in one, and as encapsulated FVPTC in two nodules with or without capsular invasion. In contrast, only one out of six nodules diagnosed as follicular neoplasm in the study group was finally diagnosed as noninvasive encapsulated FVPTC after an additional IHC staining and further evaluation of permanent sections. The other nodule was diagnosed as oncocytic PTC after further evaluation of the remaining specimen.

Deferred lesions or lesions of follicular neoplasm that are finally confirmed to be malignant on permanent sections need to undergo secondary surgical procedure or other additional treatment. As such, we should note that 80% of the follicular neoplasms and 67% of the deferred lesions in the control group were finally confirmed to be malignant, whereas 33% of the follicular neoplasms in the study group were finally confirmed to be malignant. In the control group, two patients diagnosed with follicular neoplasm underwent completion thyroidectomy and two times of radioiodine treatment. Three patients whose frozen diagnoses were deferred underwent additional radioiodine treatment. On the other hand, three patients in the study group, diagnosed as FVPTC (n = 2) and lymphocytic thyroiditis (n = 1), avoided secondary surgical procedure.

We do have two nodules (3.7%) in the study group that could not be diagnosed even with the aid of IHC, which is only natural because patterns of immunoreexpression in FVPTC can vary even in permanent sections.<sup>11-13</sup> But, if we consider the fact that the number escalates to six (7.0%) in the control group without the aid of IHC, we can safely say that the IHC can make a rather significant difference in the accuracy of frozen diagnosis in follicular patterned lesions. Therefore, we propose that if more specific antibodies are selected and applied, an intraoperative IHC stain on frozen sections can significantly improve the diagnostic accuracy in thyroid follicular lesions.

In conclusion, although the significance of intraoperative IHC stain is somewhat compromised by longer turnaround time, it considerably diminishes the diagnostic discrepancy and inaccuracy. With consideration of the adverse effects of indefinite intraoperative diagnosis or discrepancy between the frozen and permanent diagnoses incurred on the patients, a development of more specific antibodies is necessary and their application to the intraoperative

diagnosis of thyroid follicular lesions will further increase the diagnostic accuracy.

### Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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