Interobserver and Intraobserver Variation Among Experts in the Diagnosis of Thyroid Follicular Lesions With Borderline Nuclear Features of Papillary Carcinoma

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Abstract

Distinguishing follicular variant of papillary carcinoma (FVPC) from follicular adenoma and follicular carcinoma can be difficult if nuclear features of papillary carcinoma are not well developed or only focally present. We assessed interobserver and intraobserver agreement among 6 thyroid experts by using 15 cases in which original pathologists suspected FVPC. There was unanimous expert agreement in diagnosing FVPC in only 2 cases (13%) and majority agreement in 6 cases (40%). Unanimous agreement on benign and malignant diagnoses was seen in 4 cases (27%) and majority agreement on malignancy in 8 cases (53%). Intraobserver agreement ranged from 17% to 100%. Histologic features considered most helpful in diagnosing FVPC were nuclear clearing, nuclear grooves, nuclear overlapping and crowding, nuclear membrane irregularity, and nuclear enlargement. This considerable interobserver and intraobserver variability in the diagnosis of FVPC seems to result from lack of agreement on the minimal criteria needed to diagnose FVPC, even among experts.

There has been growing concern recently regarding the possibility of underdiagnosis of cases of follicular variant of papillary carcinoma (FVPC) as benign neoplastic or nonneoplastic lesions. This concern is partially due to reports of rare cases of FVPC originally diagnosed as follicular adenoma (FA) or nodular hyperplasia but later having lung and bone metastases and partially due to litigation concerns for missing a diagnosis of FVPC.[1-3] Similarly, the overdiagnosis of a given encapsulated follicular epithelial lesion or neoplasm as FVPC is problematic.

FVPC can be easily diagnosed when nuclear features of papillary carcinoma (NFPC) are classic and diffusely distributed throughout the tumor. Distinguishing FVPC from FA and follicular carcinoma (FC), however, can be extremely difficult if NFPC are not well developed or are only focally expressed. Currently, there are no well established or reproducible minimal criteria for the diagnosis of FVPC in these borderline cases, which has resulted in many of these cases being sent to thyroid pathology experts for outside consultation. However, there may be significant disagreement with the primary pathologist's diagnosis at the time of consultation or on retrospective review. Patient management may be greatly affected by the discrepant diagnoses because treatment ranges from lobectomy for FA to total thyroidectomy with or without radioactive iodine 131 (^{131}I) for FC and FVPC. This study was undertaken to evaluate the degree of concordance among expert pathologists in the evaluation of thyroid follicular tumors with borderline NFPC (ie, quantitative and/or qualitative changes) and to assess the diagnostic criteria considered most helpful in establishing the diagnosis.

Materials and Methods

We searched the files of PA Labs and Ball Memorial Hospital (community-based private practice), Muncie, IN, for thyroid lesions in which the original pathologists (general anatomic pathology/clinical pathology board-certified pathologists) considered the differential diagnosis of FVPC vs FA or FC and sought outside consultation for a definitive diagnosis. We selected 15 cases for this study **Table 1**. Of the 15 cases, 4 had initially been sent by the original pathologist to more than one outside consultant (cases 5, 7, 9, 10).

For the purpose of this study, 1 or 2 representative H&E-stained glass slides from each case and a brief clinical history were circulated to 6 internationally renowned pathologists with expertise in thyroid pathology (S.L.A., J.K.C.C., R.A.D., C.S.H., V.A.L., and B.M.W.). The expert pathologists were asked to choose from the following list of diagnoses: FA, FC, FVPC, or other benign lesion. Diagnoses given as "follicular neoplasm with questionable invasion/suspicious for FC" or "well-differentiated thyroid tumor of uncertain malignant potential" were categorized as FA for statistical purposes. The experts were also instructed to list, in descending order, the 4 most important observed histologic and cytologic criteria that enabled them to reach a diagnosis of FVPC in each case and document the presence of capsular (partial or complete) and/or vascular invasion, when present. In search of "standout" histologic features recognized by the experts, the diagnostic criteria listed in cases with majority agreement (4 or more experts agreed) were tabulated and compared with the criteria generated from cases with nonmajority agreement (3 or fewer experts agreed). For each case, the experts were also asked to state how the patient would have been treated at their institution (no further surgery or lobectomy only, total or subtotal thyroidectomy, or total thyroidectomy + ^{131}I ablation).

The same glass slides were recirculated (with different labels and in different order) among the experts, 10 to 15 months later, to assess intraobserver agreement.

The follow-up period ranged from 7 to 13 years (mean, 7.6 years). Completion thyroidectomy performed on case 7 revealed a 1.3-cm classic papillary thyroid carcinoma (PTC) with prominent papillary architecture, limited to the thyroid (Table 1). None of the patients had evidence of tumor recurrence or developed lymph node or distant metastasis.

Results

A complete listing of diagnoses made by the 6 experts is given in **Table 2**. The experts were assigned random numbers, which were unrelated to their listed alphabetical order as coauthors. There was complete agreement among all 6 in only 2 cases (13%): FVPC (case 7) and lymphocytic thyroiditis (case 2) **Image 1**. It is interesting that the unanimous agreement on malignancy occurred in the only case that demonstrated definite malignancy on follow-up: classic PTC **Image 2** in contralateral completion thyroidectomy (case 7, Table 1).

There was a majority agreement (among 4 or more experts) on the diagnosis of FVPC in 6 (40%) of 15 cases. When diagnoses were categorized as benign (FA, nodular goiter, or lymphocytic thyroiditis) or malignant (FC or FVPC), agreement among all 6 experts was seen in 4 cases (27%; cases 2, 4, 7, and 15). Majority agreement on malignant diagnoses was demonstrated in 8 cases (53%) **Table 3**. These results indicated that the experts had widely different

Table 1
Clinicopathologic Features of Examined Cases of Thyroid Follicular Lesions

Case No./Sex/ Age (y)	Size (cm)	Surgery	Diagnosis of Primary Pathologist	Outside Consultation	Follow-up
1/F/30	3.0	TT	FN "suspicious" for FVPC	Well-differentiated FN	NER, 11 y
2/F/59	0.6	PT	Hashimoto thyroiditis, suspicious for FVPC	Hashimoto thyroiditis	NER, 12 y
3/F/30	3.3	PT	FVPC vs FA	FA	NER, 11 y
4/F/23	3.8	PT	FC, minimally invasive	FC	CT; NER, 10 y
5/M/49	4.2	PT	Favor FA, cannot exclude FVPC	FVPC (2 consultants); FA (1 consultant)	CT; NER, 8 y
6/F/51	2.5	PT	FA, suspicious for vascular invasion	FA	NER, 8 y
7/M/44	1.4	PT	FVPC	FA, FVPC	CT, 1.3-cm PTC; NER, 7 y
8/F/49	0.9	PT	FA vs FVPC	FVPC	NER, 6 y
9/F/38	3.0	PT	FA vs FC	FA (2 consultants); FVPC (1 consultant)	NER, 9 y
10/F/53	2.0	PT	FA	FVPC (2 consultants)	CT; NER, 7 y
11/M/31	4.0	PT	FA vs FVPC	FA	NER, 6 y
12/F/32	2.6	PT	Favor FVPC	FVPC	CT; NER, 8 y
13/F/58	2.8	PT	FA	FVPC	NER, 13 y
14/F/30	2.5	PT	FA vs FC	FVPC	CT; NER, 7 y
15/F/69	2.9	PT	FA vs FC	FC	CT; NER, 9 y

CT, completion total thyroidectomy; FA, follicular adenoma; FC, follicular carcinoma; FN, follicular neoplasm; FVPC, follicular variant of papillary carcinoma; NER, no evidence of malignant recurrence or metastasis; PT, partial thyroidectomy (lobectomy); PTC, papillary thyroid carcinoma; TT, total thyroidectomy + iodine 131.

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thresholds for making a diagnosis of FVPC **Image 3**. Expert 6, for example, had the lowest FVPC diagnosis rate (2 of 15 cases), suggesting use of the strictest criteria among the group **Table 4**. Expert 5, on the other hand, had the highest FVPC diagnosis rate (14 of 15 cases), suggesting use of more liberal criteria. There was unanimous agreement among experts on the presence of definitive capsular invasion in only 1 of 10 cases (10%; case 4), but there was no unanimous agreement on the extent of capsular invasion (partial vs complete) or on the presence of vascular space invasion (Table 2). There was majority agreement on the presence of definite capsular and vascular invasion in 2 (20%) of 10 cases (cases 4 and 7) and 1 (25%) of 4 cases (case 4), respectively.

The histologic criteria cited by the experts to be most helpful in establishing a diagnosis of FVPC are listed in **Table 5**. There were no significant differences between the cited diagnostic criteria for cases with and without majority expert agreement.

Table 2
Diagnoses Made by Expert Pathologists in 15 Cases of Thyroid Follicular Lesions

	Expert											
	1		2		3		4		5		6	
Case No.	Diagnosis	Inv	Diagnosis	Inv	Diagnosis	Inv	Diagnosis	Inv	Diagnosis	Inv	Diagnosis	Inv
1	FVPC	CI	FA	—	FA	—	FA	—	FVPC	—	FA	—
2	Benign	—	LT	—	LT	—	LT	—	LT	—	HN, LT	—
3	FVPC	—	FVPC	—	FVPC	CI	FA	—	FVPC	CI, ?VI	FN	?CI
4	FC	CI/c	FC	CI/c, VI	FVPC	CI, VI	FC	CI/c, VI	FVPC	CI	FC	CI/p, VI
5	Benign	—	HN	—	FA	—	HN	—	FVPC	—	FA	—
6	FA	—	FA	—	FVPC	—	FVPC	—	FVPC	—	FA	—
7	FVPC	CI	FVPC	CI	FVPC	CI	FVPC	—	FVPC	CI, ?VI	FVPC	—
8	FC	CI/p	FA	—	FVPC	—	FA	—	FVPC	CI	FN	?CI
9	FC	CI	FVPC	—	FVPC	—	FA	—	FVPC	CI/p	FA	—
10	FVPC	—	FVPC	—	FVPC	—	FA	—	FVPC	—	FA	—
11	Benign	—	FA	—	FVPC	—	HN	—	FVPC	—	FA	—
12	Benign	—	FVPC	—	FVPC	—	HN	—	FVPC	CI	FA	—
13	FVPC	—	FVPC	CI	FVPC	—	FA	—	FVPC	CI	FN	?CI/p
14	FA	—	FVPC	—	FVPC	—	FVPC	—	FVPC	CI/p	FVPC	—
15	FVPC	CI, VI	FC	CI, VI	FVPC	—	FVPC	—	FVPC	?CI, ?VI	FC	VI

CI, capsular invasion; CI/c, complete capsular invasion; CI/p, partial capsular invasion; FA, follicular adenoma; FC, follicular carcinoma; FN, follicular neoplasm; FVPC, follicular variant of papillary carcinoma; HN, hyperplastic nodule; Inv, invasion; LT, lymphocytic thyroiditis; VI, vascular invasion; ?, questionable.

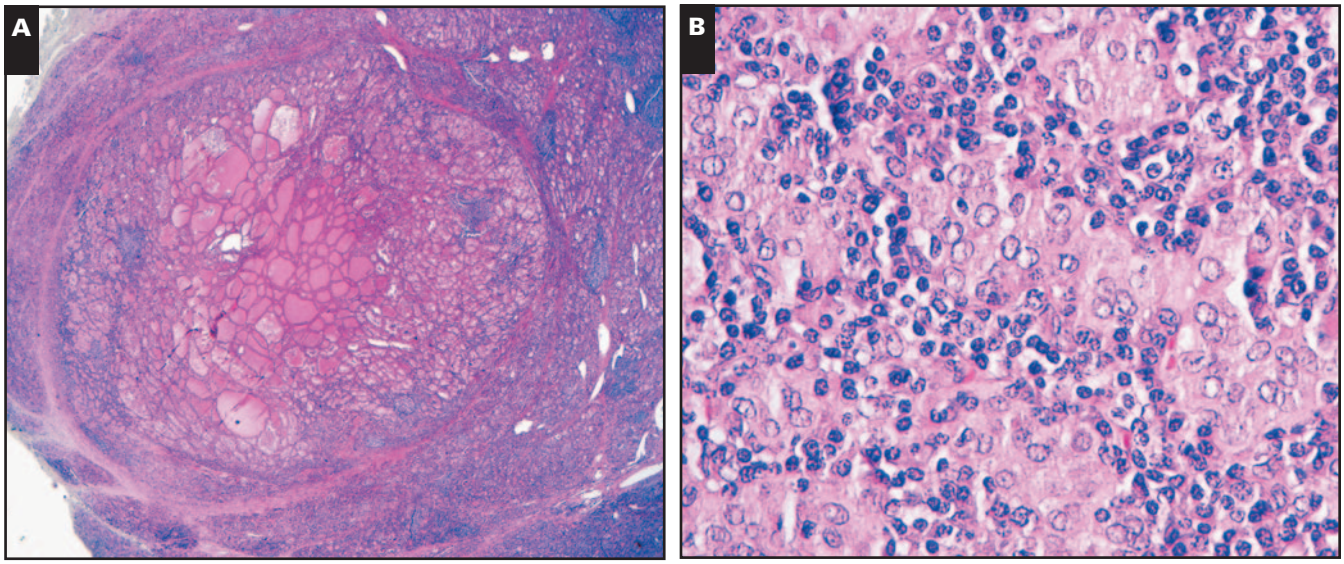

Image 1 (Case 2) Lymphocytic thyroiditis. There was complete agreement among all experts in this case. **A**, A 0.6-cm distinct nodule in a background of lymphocytic thyroiditis (H&E, ×20). **B**, High power shows nuclear clearing and occasional grooves, but nuclear features of papillary carcinoma were deemphasized in the presence of lymphocytic thyroiditis (H&E, ×600).

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Intraobserver agreement in the diagnosis of FVPC and malignancy ranged from 17% to 100% and 60% to 100%, respectively **Table 6** and **Table 7**. Expert 4, for example, had the lowest intraobserver agreement rate in diagnosing FVPC (1/6 [17%]; Table 6). Expert 1 had an intraobserver agreement rate of 73% (11/15 cases) when establishing a benign vs malignant diagnosis (Tables 6 and 7). Expert 5 showed 100% intraobserver agreement rate in diagnosing FVPC and malignancy, but this was related to a high malignancy rate (14 of 15 cases).

There was general agreement among the experts on patient management strategies, so this factor apparently did

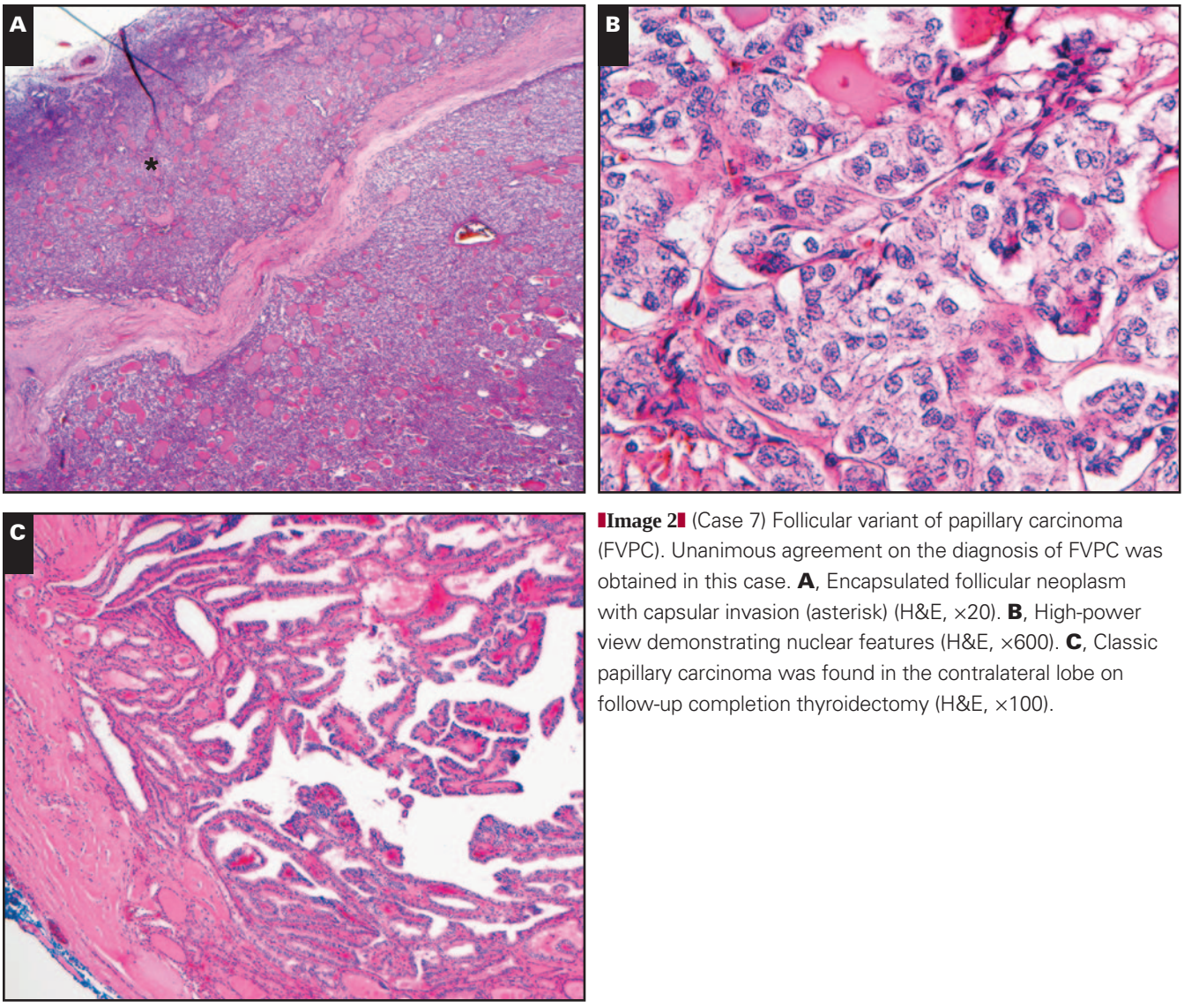

Image 2 (Case 7) Follicular variant of papillary carcinoma (FVPC). Unanimous agreement on the diagnosis of FVPC was obtained in this case. **A**, Encapsulated follicular neoplasm with capsular invasion (asterisk) (H&E, ×20). **B**, High-power view demonstrating nuclear features (H&E, ×600). **C**, Classic papillary carcinoma was found in the contralateral lobe on follow-up completion thyroidectomy (H&E, ×100).

Table 3
Interobserver Expert Agreement in Diagnoses of FVPC and Malignancy in 15 Cases*

Expert Agreement	FVPC	Malignancy
6 of 6	1 (7)	3 (20)
5 of 6	1 (7)	1 (7)
4 of 6	4 (27)	4 (27)
3 of 6	3 (20)	3 (20)
2 of 6	4 (27)	2 (13)
Majority (≥4 experts)	6 (40)	8 (53)

FVPC, follicular variant of papillary carcinoma.
* Malignancy is follicular carcinoma or FVPC. Data are given as number (percentage).

Table 4
Comparison of Rates of Malignant and Benign Diagnoses Made by Experts on First Review in 15 Cases*

Expert	FVPC	FC	Malignant	Benign
1	6 (40)	3 (20)	9 (60)	6 (40)
2	7 (47)	2 (13)	9 (60)	6 (40)
3	12 (80)	0 (0)	12 (80)	3 (20)
4	4 (27)	1 (7)	5 (33)	10 (67)
5	14 (93)	0 (0)	14 (93)	1 (7)
6	2 (13)	2 (13)	4 (27)	11 (73)

FC, follicular carcinoma; FVPC, follicular variant of papillary carcinoma.
* Data are given as number (percentage).

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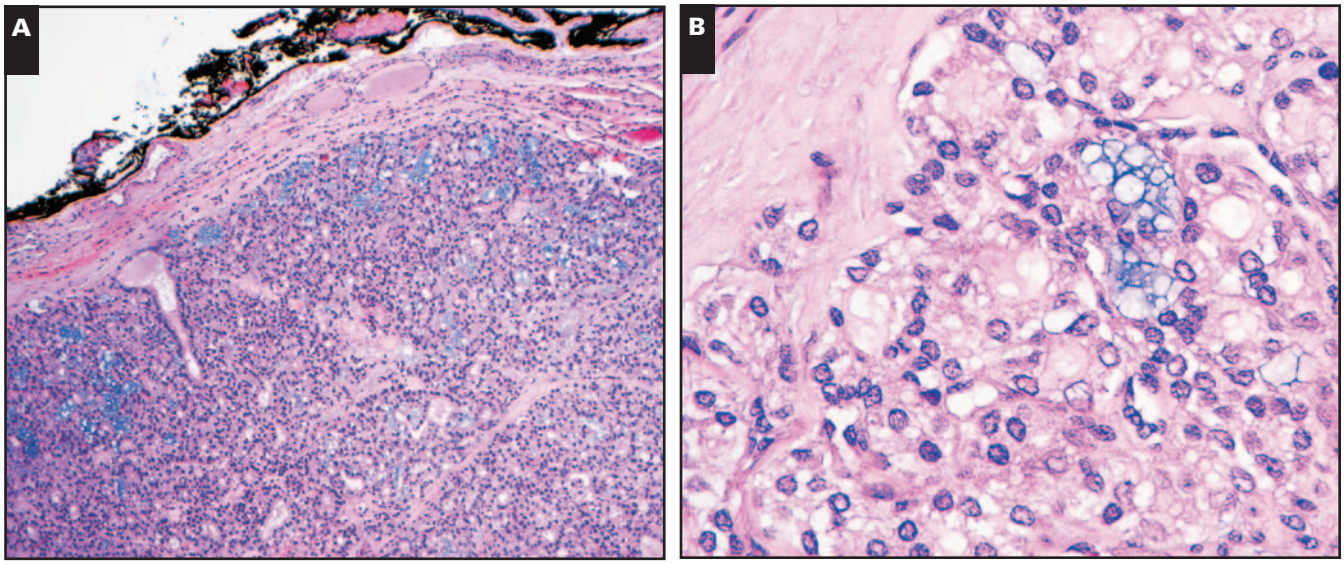

Image 3 (Case 1) Of 6 experts, 2 made a diagnosis of follicular variant of papillary carcinoma (FVPC), and the other 4 diagnosed this lesion as follicular adenoma and noted that the presence of some nuclear features of papillary carcinoma were insufficient to establish a diagnosis of FVPC. **A**, Low power showed an encapsulated follicular neoplasm (H&E, ×100). **B**, High power showed scattered nuclear irregularity, grooves, overlapping, and clearing (H&E, ×600).

not significantly contribute to the variations in diagnoses. Most experts indicated that total thyroidectomy with or without ^{131}I ablation would be indicated in their respective institutions for FVPC measuring 1.0 cm or greater and for FC with vascular invasion and/or complete capsular invasion. Some experts further qualified that only lobectomy may be the treatment of choice at some institutions for FC with partial capsular invasion, totally encapsulated FVPC, or for low-risk tumors (ie, small tumor, female patient, and age younger than 50 years).

Table 5
Diagnostic Criteria for Follicular Variant of Papillary Carcinoma as Cited by Experts*

Histologic Criteria	Majority Agreement Cases (n = 6)†	Nonmajority Agreement Cases (n = 8)
Nuclear clearing	1	1
Nuclear grooves	2	3
Nuclear overlapping	3	5
Nuclear irregularity	4	2
Nuclear enlargement	5	7
Chromatin margination	6	4
Distorted follicle architecture	7	10
Nuclear elongation	8	6
Intranuclear pseudoinclusions	9	9
Fibrosis/sclerosis	10	—
Scalloped colloid or abortive papillae	11	11
Multiple nucleoli	12	8
Increased cellularity	13	—

* Ranked in descending order of importance.
† Majority agreement: 4 or more experts agreed.
‡ Nonmajority agreement: 3 or fewer experts agreed.

Discussion

The major differential diagnoses of an encapsulated thyroid nodule with follicular architecture include adenomatous hyperplasia, FA, FC, and FVPC. The diagnosis of FVPC is straightforward when characteristic NFPC are seen diffusely throughout the tumor.[4] It may be extremely difficult, however, to distinguish FVPC from FA or FC when NFPC are not well developed or seen only focally.[5] Microdissection experiments have demonstrated *RET/PTC* rearrangements to be restricted to these foci, which may be interpreted as confirmatory of PTC or possibly representing early development of PTC in a preexisting benign lesion.[6-8] Controversy, however, still exists regarding the clinical significance of follicular neoplasms with borderline NFPC. Some investigators believe that these neoplasms are associated with an excellent outcome and, therefore, should be classified as benign neoplasms or tumors of undetermined malignant potential to avoid unnecessary therapy.[6,9,10] Others believe that these neoplasms should be classified as FVPC and staged and treated accordingly.[5] Many of these borderline cases are sent to expert consultants for opinion. It is believed that encapsulated FVPC represents the single most common source of outside consultation in thyroid pathology today.[6]

Some authors have raised alarms regarding an increasing tendency to overdiagnose FVPC.[1,11] This may be, in part, due to lowering the threshold for the diagnosis of FVPC based on the occasional cases developing metastasis on follow-up.[1,11] Baloch and LiVolsi[2] reported 5 encapsulated follicular neoplasms that exhibited multifocal NFPC and developed distant bone metastases. In 3 of those cases, bone metastases arose 7 to 17 years following resection of lesions diagnosed

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Table 6
First vs Second Diagnosis Made by Experts in 15 Cases of Thyroid Follicular Lesions

	Expert 1		Expert 2		Expert 3		Expert 4		Expert 5		Expert 6	
Case No.	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
1	FVPC	FVPC	FA	FA	FA	FA	FA	FA	FVPC	FVPC	FA	FA
2	Benign	NN	LT	NN	LT	NN	LT	NN	LT	NN	HN, LT	NN
3	FVPC	NN	FVPC	FVPC	FVPC	FVPC	FA	FVPC	FVPC	FVPC	FN	FA
4	FC	FA	FC	FC	FVPC	FC	FC	FC	FVPC	FVPC	FC	FC
5	Benign	FA	HN	NN	FA	NN	HN	NN	FVPC	FVPC	FA	FA
6	FA	FA	FA	FA	FVPC	FVPC	FVPC	NN	FVPC	FVPC	FA	FA
7	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC
8	FC	FC	FA	FA	FVPC	FVPC	FA	FC	FVPC	FVPC	FN	FA*
9	FC, NOS	FC	FVPC	FVPC	FVPC	FVPC	FA	FA	FVPC	FVPC	FA	FA*
10	FVPC	FA	FVPC	FA	FVPC	FVPC	FA	NN	FVPC	FVPC	FA	FA
11	Benign	NN	FA	FA	FVPC	FVPC	HN	NN	FVPC	FVPC	FA	FA
12	Benign	NN	FVPC	FVPC	FVPC	FVPC	HN	NN	FVPC	FVPC	FA	FA
13	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	FA	FVPC	FVPC	FVPC	FN	FC
14	FA	FVPC	FVPC	FVPC	FVPC	FVPC	FVPC	NN	FVPC	FVPC	FVPC	FA
15	FVPC	FVPC	FC	FC	FVPC	FVPC	FVPC	FA	FVPC	FVPC	FC	FC

FA, follicular adenoma; FC, follicular carcinoma; FN, follicular neoplasm; FVPC, follicular variant of papillary carcinoma; HN, hyperplastic nodule; LT, lymphocytic thyroiditis; NN, nonneoplastic; NOS, not otherwise specified.
* The terminology "well-differentiated thyroid tumor of uncertain malignant potential" was suggested.

originally as FA. In retrospect, however, these 3 cases had evidence of vascular invasion. In another case, capsular invasion was demonstrated but was subtle enough to be overlooked.[2] Others have reported the macrofollicular variant of PTC that closely resembled benign nodular goiter on histologic examination but had regional lymph node or distant lung and bone metastases.[3,12] These reports have driven pathologists to make every attempt not to miss a diagnosis of FVPC. For surgeons and endocrinologists, it is also safer to overdiagnose and overtreat than to underdiagnose and undertreat.[1] Chan[11] and Rosai[6] advocated the application of strict criteria in the diagnosis of FVPC and argued that it is fully justified to err on the benign side in uncertain cases because the prognosis is excellent and simple excision of encapsulated FVPC is curative.

There is, to date, no agreed-on minimum histologic definition of FVPC.[13] Rosai et al[14] stated that the presence of typical ground-glass nuclei should be seen in more than an occasional number of cells before a thyroid neoplasm is classified as PTC. On the other hand, plain vesicular nuclei can be found in a wide range of benign and malignant thyroid disorders and are of no diagnostic significance by themselves.[14] However, there are no established criteria as to what percentage of a given (encapsulated) follicular lesion must show NFPC to make such a diagnosis. Several questions, therefore, need to be addressed[1]: What criteria should be applied to the nuclei of follicular lesions to qualify them as PTC? What are the quantitative criteria (ie, percentage of a given follicular lesion) required to diagnose FVPC? Which of the nuclear features are most diagnostic? What degree of nuclear pallor and how many nuclear grooves and optically clear nuclei are required before issuing a diagnosis of FVPC?

Table 7
Intraobserver Agreement Among Experts*

Expert	FVPC	FC	Malignant vs Benign
1	4/7 (57)	2/3 (67)	11/15 (73)
2	6/7 (86)	2/2 (100)	14/15 (93)
3	11/12 (92)	0/1 (0)	15/15 (100)
4	1/6 (17)	1/2 (50)	9/15 (60)
5	14/14 (100)	0/0 (0)	15/15 (100)
6	1/2 (50)	2/3 (67)	13/15 (87)

FC, follicular carcinoma; FVPC, follicular variant of papillary carcinoma.
* Data are given as number/total (percentage).

We undertook this study to evaluate the degree of concordance among expert pathologists in the diagnosis of thyroid follicular tumors with borderline NFPC and the diagnostic criteria that they used. This study demonstrated that there was marked interobserver variation. There was complete agreement among all 6 experts in only 2 cases (13%). One of those cases (case 7) was signed out by the original pathologist as FVPC, but conflicting opinions of FA and FVPC were received from outside consultants at that time. It is interesting that this case with unanimous agreement on a diagnosis of FVPC (Image 2) was the only case that demonstrated definite malignancy on follow-up: classic PTC in contralateral completion thyroidectomy (case 7, Table 1). The other case was unanimous agreement on benignity, in which the lesion showed borderline NFPC in association with lymphocytic thyroiditis (Image 1), suggesting that all experts used a higher threshold for diagnosing PTC in that setting. This finding is not surprising because it is well recognized that follicular cells in proximity to lymphocytic infiltrate can show marked nuclear clearing and occasional nuclear grooves, mimicking PTC.[15-18]

There was a majority agreement (4 or more experts) on the diagnosis of FVPC in 6 (40%) of 15 cases. In this study, the

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primary histologic features used by the experts for diagnosing FVPC were, in descending order, nuclear alterations, including clearing and/or very fine (powdery) chromatin, nuclear grooves, nuclear overlapping and crowding, nuclear membrane irregularity, and nuclear enlargement. Secondary features included chromatin margination, distorted follicle architecture, and fibrosis/sclerosis (Table 5). There were no significant differences between the cited diagnostic criteria for cases with and without majority expert agreement (Image 3). This finding suggests that although the experts used similar criteria, they had varying thresholds in applying them to the diagnosis of FVPC.

This study also demonstrated wide variations in the rates of self-agreement when the same cases were reexamined. Intraobserver agreement for the diagnoses of FVPC and malignancy ranged from 17% to 100% and 60% to 100%, respectively (Table 7). Slightly higher interobserver rates were achieved when diagnoses were categorized as benign (FA or other benign) or malignant (FC or FVPC). Unanimous agreement among all experts was seen in 4 cases (27%) and majority agreement in 8 cases (53%).

Only 1 previous study, by Lloyd et al,[19] specifically evaluated interobserver variability in the diagnosis of FVPC among experts; 87 cases were reviewed by 10 experienced thyroid pathologists. In contrast with our study, only cases with 1 or more major features of PTC were retrieved for analysis (intranuclear pseudoinclusions, abundant nuclear grooves, ground-glass nuclei, enlarged overlapping and irregular nuclei, and psammoma bodies), including many cases with frank invasive features. That is, most cases showed well-developed histologic features of PTC, such that 85 of 87 cases were originally diagnosed as FVPC. Not surprisingly, the interobserver agreement was higher, in that all 10 experts agreed on the diagnosis of FVPC in 39% of cases, with majority agreement (6 of 10 experts) in 93%.[19] A subset of these tumors with clinical evidence of metastases (21 cases) showed a higher degree of concordance, including 67% agreement among all 10 experts and 100% agreement among 7 experts.[19] Most of these metastatic tumors (19 of 21) showed definite capsular and/or vascular space invasion.

Interobserver variation may also be influenced by geographic location and training background of the pathologists. Hirokawa et al[20] compared the diagnoses of 8 pathologists (4 American and 4 Japanese) who reviewed 21 encapsulated thyroid follicular lesions. There was complete agreement among all 8 pathologists in 2 cases (10%), agreement of 7 of 8 pathologists in 29% of cases, and agreement of 6 of 8 pathologists in 76% of cases.[20] All pathologists, however, agreed on the diagnosis of benign vs malignant lesion in 13 (62%) of 21 cases. The frequency of PTC diagnoses was considerably higher among American (25%) compared with Japanese (4%) pathologists, whereas the frequency of adenomatous goiter diagnoses was higher among Japanese (93%) compared with American (6%) pathologists. Two American pathologists had higher rates of PTC diagnoses (8/21 and 11/21) compared with the remaining 6 reviewers (0/21 to 1/21). Our study also demonstrated a wide variability in the individual rates of diagnosing FVPC, suggesting that the experts had different thresholds for making a PTC diagnosis. Expert 6, for example, had the lowest FVPC rate (2/15 [13%]), indicating the use of the strictest criteria among the group, and expert 5 had the highest FVPC rate (14/15 [93%]), suggesting the use of more liberal criteria (Table 4).

Although diagnosing FC was not the focus of our study, it was apparent that there were wide discrepancies among the experts in issuing such an interpretation. This is because the distinction between FA and minimally invasive FC is not always easy and often is subjective.[20] In our study, there was unanimous agreement among experts on the presence of definitive capsular invasion in only 1 (10%) of 10 cases, and there was no unanimous agreement on the extent of capsular invasion (partial vs complete) or on the presence of vascular space invasion.

Several reports found FC to be more complicated to diagnose than PTC.[20-22] Ron et al[23] reported that 4 (15%) of 27 cases originally diagnosed as thyroid cancer (including 3 of 6 FC cases) were reclassified as benign (FA or goiter) on second review by their study pathologists. From the Finnish cancer registry, Saxen et al[24] reclassified 82 (23.8%) of 345 malignant thyroid cancers as benign, including one third of FC cases. In 200 thyroid cancers reviewed from the Swedish cancer registry, Holm et al[25] reported 10.5% overdiagnosis of malignancy, with FA being the tumor most often erroneously reported as carcinoma. Franc et al[26] examined interobserver reproducibility in diagnosing FC among 5 French pathologists and reported unanimous agreement between all observers in 13 (54%) of 24 cases. Fassina et al[27] tested the level of agreement among a panel of 7 pathologists who reviewed 200 cases of thyroid tumors, using the 1988 World Health Organization classification, and found poor agreement for FC. There was unanimous agreement among the 7 pathologists in 62.5% of cases (125/200) and majority agreement (at least 4 pathologists) in 91% of the cases.[27] However, a major limitation to studies based on material retrieved from cancer registries or only on cases originally diagnosed as malignant is that an original pathologist making a clinical decision on a borderline case may issue a diagnosis that requires more intensive treatment, whereas a research pathologist may find it easier to conform to a standard classification because no patient is involved and no surgeon is pressing for an answer.[23]

Although some studies have shown immunohistochemical and molecular studies (such as high-molecular-weight cytokeratin, cytokeratin 19, galectin-3, mesothelium-associated antibody HBME-1, CD57, CITED1, fibronectin-1, CD15, CD44, platelet-derived growth factor, *BRAF* and *ras* mutations, microRNA overexpression, or *RET/PTC* translocation) to be

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helpful in confirming a diagnosis of PTC, others have found these studies not discriminatory enough to distinguish PTC from other follicular lesions.[8,11,28-35] Certainly as our understanding of the molecular basis of thyroid cancer advances, newer markers may be identified that will allow for more accurate characterization of specific subtypes of cancers. However, at present, light microscopy remains the "gold standard" to establish the diagnosis of FVPC.[35] Genetic studies further substantiate the association between encapsulated FVPC and that of FC and FA, showing similar profiles in some cases.[36] Mutations of *ras*, for example, are detected in FA, FC, and FVPC, but not in classic PTC.[34,37-41] *RET* translocation and *BRAF* mutations, on the other hand, are common in classic PTC but rare in FVPC.[34,42] In addition, the PTC cases reported to demonstrate *ras* mutations usually show less characteristic NFPC, lack extrathyroidal extension, and are associated with a low rate of lymph node metastasis and are, thus, more similar to FA and FC.[43] These findings have led some authors to argue that a high proportion of cases currently diagnosed as encapsulated FVPC actually represent FA or FC.[29,44]

One of the experts in our study (expert 6) applied the terminology of the Chernobyl Pathologists Group (CPG) to 2 cases (Table 6). The CPG proposed to classify neoplasms with questionable NFPC and absent capsular or vascular invasion as "well-differentiated tumor of uncertain malignant potential."[9] The CPG acknowledged, however, that there are dangers that such a category can be used as an easy option to avoid committing to a definite diagnosis of benign vs malignant.[9] Others believe that such a category should not be used until clinical behavior has been evaluated by long-term clinical studies and follow-up.[4] The CPG also recommended the term "well-differentiated carcinoma, not otherwise specified" for encapsulated follicular neoplasms with obvious capsular invasion but questionable NFPC.[9] The use of this nomenclature has not been generally accepted and has been the subject of considerable debate.[45]

Conclusion

It seems that in thyroid lesions in which the nuclear features of PTC are incomplete or borderline, diagnostic disagreements will frequently arise. The present study illustrates the difficulties encountered in daily practice by pathologists in evaluating such tumors.[46] Light microscopy currently remains the gold standard for the diagnosis of FVPC, but recognition of minimal features of FVPC is associated with a great deal of subjectivity. Our data, at this point, present no ideal solution to this problem because of lack of well-accepted independent means—immunohistochemical or molecular—to validate a diagnosis of PTC. There may be a need for establishing more precise qualitative and quantitative morphologic criteria (such as what constitutes nuclear alterations that are diagnostic of PTC), more rigorous application of already established criteria, or both, to improve consistency in the pathologic diagnosis.[47] These well-defined, reproducible, and agreed-on minimal criteria need to be established by experts in the field of thyroid pathology, possibly in a consensus conference or by formulation of an international classification of thyroid tumors that reflects biologic potential and clinical behavior, to help reduce the significant interobserver and intraobserver variation associated with these lesions.[1,48] These types of interobserver studies can also potentially provide a source of defense for practicing pathologists when their diagnoses are overturned by an "expert" pathologist because experts cannot agree on the diagnosis in the majority of cases.[1,49]

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