Strict Criteria Should Be Applied in the Diagnosis of Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

John K.C. Chan, MBBS

Papillary thyroid carcinoma (PTC) is defined on the basis of the cytologic features, and, thus, in contrast with follicular carcinoma, demonstration of invasion is not required to establish a diagnosis of malignancy. Although most PTCs show an admixture of papillary structures and follicles, some are composed entirely of follicles—the follicular variant of PTC. For the examples that are nonencapsulated, the diagnosis usually poses no problems, because the invasive growth and accompanying sclerosis leave no doubt about the malignant nature of the process. It is a different story for encapsulated neoplasms composed exclusively of follicles and lacking capsular and vascular invasion—the distinction between follicular adenoma and follicular variant of PTC rests on the pathologist's perception of the nuclear characteristics of the follicular cells. If the pathologist believes that the nuclear features are compatible with those of PTC, a diagnosis of malignancy (PTC) is made just on that basis. However, the nuclei very often show some but not all of the nuclear features of PTC, eg, pale nuclei alone, making a clear-cut diagnosis difficult. If the case is sent out for consultation opinion, more often than not, divergent opinions are obtained, which reflects a lack of uniform diagnostic criteria.

Managerial Considerations

Before returning to the minimum diagnostic criteria, it is helpful to consider the following implications of the diagnoses:

1. Follicular adenoma is a totally benign lesion adequately treated by nodulectomy or hemithyroidectomy.

2. The encapsulated variant of PTC, whether exhibiting papillary or pure follicular architecture, is associated with an excellent prognosis **Table 1**.[1-6] According to a number of series on encapsulated PTCs (totaling more than 100 patients), lymph node metastasis occurs in approximately 25% of cases, but distant blood-borne metastasis almost never occurs (it occurred in only 1 patient). There is no recurrence or metastasis after surgical excision, be it a hemithyroidectomy or total thyroidectomy.

Based on the aforementioned data, it is fully justified to err on the benign side when there are uncertainties in the

Table 1
Clinical Characteristics of Patients With Encapsulated Papillary Thyroid Carcinoma as Reported in the Literature

Series	No. of Cases	Lymph Node Metastasis	Distant Metastasis	Clinical Outcome
Hawk and Hazard,[1] 1976	15	3	1 (bone)	14 alive and well; 1 died of disease at 9 y
Schroder et al,[2] 1984	25	6	0	23 alive and well at 1 to 15 years; 2 died of unrelated disease
Carcangiu et al,[4] 1985	21	8	0	19 alive and well; 2 alive with disease
Evans,[3] 1987	12	1	0	12 alive and well at 10-25 y
Oyama et al,[5] 1993	9	6	NA	9 alive and well at mean follow-up of 4.4 y
Moreno et al,[6] 1996	25	3	NA	25 alive and well at mean follow-up of 9 y

NA, not available.

diagnosis.[7] It would not be a disservice to the patient even if a genuine follicular variant of PTC were misdiagnosed as follicular adenoma, because simple excision of the lesion is already curative. On the contrary, taking a liberal approach in making a diagnosis of PTC for encapsulated follicular neoplasms with indeterminate cytologic features may result in overtreatment (such as completion thyroidectomy and radioactive iodine therapy) and unnecessary psychologic trauma to patients.

Diagnostic Criteria for Encapsulated Follicular Variant of PTC

Although some immunohistochemical markers, such as high-molecular-weight cytokeratin, cytokeratin 19, vimentin, HBME1, CD57, CD15, and CD44, have been reported to be more commonly expressed in PTCs than in benign thyroid lesions, these markers are not sufficiently discriminatory to aid in the diagnosis of problematic encapsulated follicular lesions of the thyroid.[7] This is because they are not infrequently expressed only focally, even in classic PTCs.[7] Even molecular analysis for the *RET/PTC* gene translocation, a hallmark of PTC, fails to provide the definitive support for the diagnosis, because it is found in only approximately one third of all cases of PTCs on one hand, and some studies have found this gene translocation even in benign thyroid lesions on the other hand.[8,9] Thus, the "gold standard" for the diagnosis of PTC is still morphologic features, which unfortunately are highly subjective.

Since no single morphologic feature is pathognomonic of PTC, a constellation of features has to be considered. Basically, the nuclear features of PTC have to be well developed before I make a diagnosis of the encapsulated follicular variant: (1) Nuclei are ovoid rather than round. (2) Nuclei are crowded, often manifesting as lack of polarization in the cells that line a follicle. (3) Nuclei show a clear or pale chromatin pattern (nuclear clearing should not be confined to the central portion of the tumor, where artifactual bloating of the nuclei is common due to delayed fixation), or they exhibit prominent grooving. (4) Psammoma bodies are found. If 1 of these 4 features is lacking, 4 or more of the following subsidiary features have to be present for a diagnosis of encapsulated follicular variant PTC to be made: (1) presence of abortive papillae, (2) predominantly elongated or irregularly shaped follicles, (3) dark-staining colloid, (4) presence of rare nuclear pseudoinclusions, and (5) multinucleated histiocytes in lumens of follicles.

Alternative Terminology

An important impetus for overdiagnosis of encapsulated follicular variant of PTC is the litigation climate, whereby the pathologist makes this diagnosis using lax criteria to avoid being sued for missing malignancy. The actual risk is, of course, practically nonexistent because adverse outcome almost never ensues for this PTC variant.

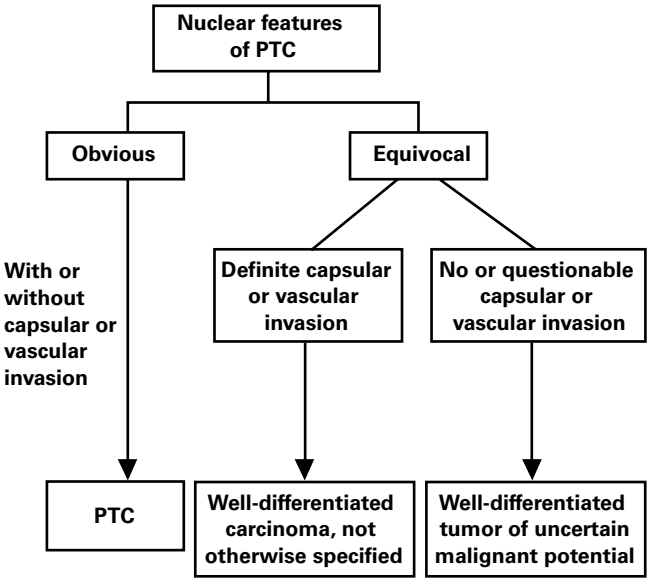

Figure 1 Nomenclature for encapsulated thyroid follicular tumors proposed by the Chernobyl pathologists group.[10] PTC, papillary thyroid carcinoma.

If there are serious concerns about litigation, it would be preferable to use the terminology proposed by the Chernobyl pathologists group **Figure 1** rather than to overdiagnose PTC.[10] Encapsulated follicular neoplasms that show some but not convincing nuclear features of PTC are diagnosed as *well-differentiated thyroid tumor of uncertain malignant potential* when capsular or vascular invasion is absent or equivocal, and *well-differentiated thyroid carcinoma, not otherwise specified* when there is definite capsular or vascular invasion (the problem being distinction between PTC and follicular carcinoma).

From the Department of Pathology, Queen Elizabeth Hospital, Kowloon, Hong Kong, SAR People's Republic of China.

Address reprint requests to Dr Chan: Dept of Pathology, Queen Elizabeth Hospital, Wylie Rd, Kowloon, Hong Kong, SAR People's Republic of China.

References

1. Hawk WA, Hazard JB. The many appearances of papillary carcinoma of the thyroid. *Cleve Clin Q*. 1976;43:207-215.
2. Schroder S, Bocker W, Dralle H, et al. The encapsulated papillary carcinoma of the thyroid: a morphologic subtype of the papillary thyroid carcinoma. *Cancer*. 1984;54:90-93.

3. Evans HL. Encapsulated papillary neoplasms of the thyroid: a study of 14 cases followed for a minimum of 10 years. *Am J Surg Pathol.* 1987;11:592-597.
4. Carcangiu ML, Zampi G, Pupi A, et al. Papillary carcinoma of the thyroid: a clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer*. 1985;55:805-828.
5. Oyama T, Ishida T, Ishii K, et al. Encapsulated papillary carcinoma of the thyroid gland: clinicopathological and cytofluorometric study in comparison with non-encapsulated papillary carcinoma. *Acta Pathol Jpn*. 1993;43:516-521.
6. Moreno A, Rodriguez JM, Sola J, et al. Encapsulated papillary neoplasm of the thyroid: retrospective clinicopathological study with long term follow up. *Eur J Surg*. 1996;162:177-180.
7. Chan JKC. Tumors of the thyroid and parathyroid glands. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumors*. 2nd ed. Edinburgh, Scotland: Churchill Livingstone; 2000:959-1056.
8. Sugg SL, Ezzat S, Zheng L, et al. Oncogene profile of papillary thyroid carcinoma. *Surgery*. 1999;125:46-52.
9. Wirtschafter A, Schmidt R, Rosen D, et al. Expression of the *RET/PTC* fusion gene as a marker for papillary carcinoma in Hashimoto's thyroiditis. *Laryngoscope*. 1997;107:95-100.
10. Williams ED, Abrosimov A, Bogdanova T, et al. Guest editorial: two proposals regarding the terminology of thyroid tumors. *Int J Surg Pathol*. 2000;8:181-183.

HOLOGIC®

First and Only FDA Cleared
Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager

Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System

Click or Scan
to discover more

genius™
DIGITAL DIAGNOSTICS