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Follicular Variant of Papillary Thyroid Carcinoma: Hybrid or Mixture?

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The prognosis of the follicular variant of papillary thyroid carcinoma (FVPTC) falls between that of classical papillary thyroid carcinoma (cPTC) and follicular thyroid carcinoma (FTC) (1). FVPTC has lower mortality and less frequent distant metastases than FTC, but higher mortality and more frequent distant metastases than cPTC. FVPTC has fewer lymph node metastases and less frequent infiltrative disease and extrathyroidal extension than cPTC, but more than FTC. But is it a hybrid disease or a mixture of diseases? The pathological appearance of a follicular-patterned tumor with the nuclear features of cPTC suggests that FVPTC is a hybrid. However, the heterogeneous nature of the disease and the mutational profile of FVPTC strongly suggest that it is a mixture of diseases (2). It is the intersection of classical descriptive pathology and modern molecular biology that permits an understanding of this group of diseases.

FVPTC is a particularly vexing entity. Initially thought to be a rare disorder, it now comprises 30% of all PTCs (3). In the 1990s, when a fine-needle aspiration biopsy (FNAB) revealed a follicular neoplasm, the most common malignancy found was FTC, with <5% being FVPTC. Now, >50% of the malignancies in this setting are FVPTC (2). Although the annual incidence of FTC has remained fairly steady over recent decades (4), the percentage of follicular-patterned thyroid malignancies that are FVPTC has steadily risen such that FVPTC makes up 85% of all follicular-patterned thyroid carcinomas (5). Yet, the pathological diagnosis of FVPTC is somewhat elusive. Careful studies involving leading thyroid pathologists suggest that these clinicians often cannot agree with each other (6) and often disagree with themselves when re-reading specimens (7).

Liu *et al*. (8) separated FVPTC into two major classes: infiltrative (invasive) and encapsulated. This classification provides a clear explanation for the disparate literature reports of outcomes in FVPTC. The infiltrative tumors were more likely to have extrathyroidal extension and lymph node metastases, and behaved in general like cPTC. The encapsulated FVPTC behaved more like follicular tumors. The encapsulated, noninvasive tumors behaved in an indolent fashion, similar to follicular adenomas. However, the encapsulated tumors with capsular or vascular invasion behaved more like FTC.

Subsequent studies of the molecular biology of these tumors further cemented the distinction between tumor groups in FVPTC. The most common mutation in cPTC is $BRAF^{V600E}$ (9). Follicular adenomas and FTC do not harbor this mutation (9). The most common mutations in follicular adenomas and FTC are the *RAS* mutations (9). *RAS* mutations are virtually never found in cPTC. When a follicular tumor is removed, the distinction between a (benign) follicular adenoma and a FTC depends upon the presence or absence of capsular or vascular invasion. Absent these features, the tumors are called benign. The infiltrative FVPTC often have *BRAF* mutations, whereas the encapsulated FVPTC most commonly have *RAS* mutations (10). These observations lend further support to the distinction between cPTC-like FVPTC and follicular tumor–like FVPTC. These authors also suggest that fully encapsulated FVPTC behave in a benign or indolent fashion, although they were not willing to state that the fully encapsulated tumors were benign.

If one accepts the fact that *RAS*-mutant tumors are follicular tumors and the distinction between follicular adenomas and follicular carcinomas requires capsular or vascular invasion, the logical assumption is that *RAS*-mutant noninvasive encapsulated tumors are benign follicular adenomas.

The Cancer Genome Atlas for PTC provides a genetic landscape for PTC, and clearly separates those PTC with *BRAF* mutations (or *BRAF*-type gene expression) from those with *RAS* mutations (or *RAS*-like gene expression), lending strong support to the thesis that FVPTC with *BRAF* mutations and FVPTC with *RAS* mutations are separate, distinct entities (11).

Given the somewhat larger size of many FVPTC compared with cPTC, clinicians often treat FVPTC as more aggressive tumors. The initial operation for many of these patients is a hemi-thyroidectomy (given atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS] or follicular neoplasm cytopathology). Therefore, many of these patients are subjected to completion thyroidectomy and radioactive iodine therapy.

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An important recent publication (12) accepts and supports the thesis that not all FVPTC behave as malignant tumors. The authors conclude that noninvasive encapsulated (or circumscribed) FVPTC behave in an indolent fashion, and therefore should not be considered malignant. The proposed new name (noninvasive follicular tumor with papillary-like nuclear features) is a mouthful but fortunately lends itself to the acronym NIFTP. The implication is that NIFTP are actually benign tumors or behave as benign tumors. Additional long-term studies will be necessary to confirm this strong impression.

This new classification has many important ramifications. There are obvious beneficial psychological and fiscal (including insurance) advantages to not having a cancer diagnosis. Are there any disadvantages to calling these tumors benign or NIFTP? There are rare cases of encapsulated FVPTC (or indeed tumors called benign follicular adenomas) that subsequently present with metastatic disease (13). Fortunately, these are extremely rare, estimated to be 0.6% of encapsulated noninvasive FVPTC (12). It is likely that patients with a NIFTP diagnosis will no longer be followed by endocrinologists who might be alert to the exceptional case. One potential strategy would encourage endocrinologists to follow very large NIFTP (e.g., tumors >5 cm) that might be more likely to behave in an aggressive fashion by monitoring serum thyroglobulin. A rising thyroglobulin would be expected to herald the presence of distant metastatic disease. Obviously, such metastases would have occurred prior to tumor removal and could not be prevented. However, the thyroglobulin monitoring approach might permit the diagnosis of metastatic disease when the tumor burden is still small. This is an as yet untested approach.

Another dilemma is what to do with the patients who were previously diagnosed with FVPTC who now fall into the NIFT category. It is of course reasonable to discuss the new diagnostic category with these patients. Whether reclassification would have insurance (including life-insurance) benefits is unknown. The psychological implications of reclassification are uncertain, and prompted Nikiforav *et al.* (12) to include a psychiatrist in their deliberations. The re-diagnosis concern is the mirror image of the dilemma faced by Widder *et al.* (14). On review of 185 follicular-patterned tumors operated on between 1993 and 2003, 25% of the tumors were reclassified; 19% had a change of diagnosis from benign to malignant, with most of the malignant tumors now being called FVPTC. After much soul-searching, the authors contacted all the patients, told them of the new diagnosis, and restaged them. Despite nonaggressive initial treatment, none of the patients re-diagnosed as having malignant tumors had evidence of residual tumor, further supporting the new NIFTP classification.

Although indeterminate FNAB with *RAS* mutations require surgery (15,16), given the NIFTP classification, they may no longer ''require'' a total thyroidectomy. In addition, in the era of NIFTP, the risk of malignancy in the various thyroid FNAB Bethesda classification categories will be correspondingly lower. Data based on 6943 FNABs (17) suggest that the risk of malignancy in AUS/FLUS declines from 31% to 17.6%, in follicular neoplasm/suspicious for follicular neoplasm from 33% to 18%, in suspicious for malignancy from 82.7% to 59.2%, and in benign FNAB coming to surgery from 9.4% to 5.9%. It is as yet uncertain what impact the NIFTP classification will have on the positive and negative predictive value of mutational analysis, gene-expression classifiers, or miRNA analysis for indeterminate thyroid FNAB. The long-term safety of following *RAS*-mutant tumors with benign FNABs is unknown.

However, the NIFTP category provides a solution to only one of the FVPTC mixture of tumors. Initial studies, based on a limited number of patients, suggested that *BRAF* mutations are uncommon in FVPTC (2). However, recent studies suggest that almost one third of FVPTC (18,19) harbor *BRAF* mutations (usually *V600E*). Given the unique association between $BRAF^{V600E}$ mutations and cPTC, it is logical to move into the modern era and treat FVPTC with *BRAF* mutations as cPTC and classify them as cPTC with follicular architecture.

Encapsulated (or well-circumscribed) FVPTC without capsular or vascular invasion behave like follicular adenomas and are now termed NIFTP. *RAS* mutations are found in more than one third of FVPTC (18,20). How should we classify *RAS*-mutant encapsulated FVPTC with capsular or vascular invasion? It is reasonable to suggest that these be considered FTC and treated as such. It is clear that many FTC with capsular invasion alone or at most a few blood vessels invaded (so-called minimally invasive FTC) behave in an indolent fashion (21,22). Some institutions do not treat minimally invasive FTC aggressively and do not insist on completion thyroidectomy or radioactive iodine therapy after hemi-thyroidectomy. On the other hand, encapsulated FVPTC with extensive vascular invasion behave as angio-invasive FTC with a high risk for distant metastatic disease (23). These patients clearly require radioactive iodine therapy. Since the encapsulated invasive FVPTC with *RAS* mutations behave as FTC, we should consider renaming them FTC with nuclear atypia.

How about FVPTC that are not readily classified? It is reasonable to assume that FVPTC with *RET/PTC* rearrangements, extrathyroidal extension, or nodal metastases will behave as cPTC. FVPTC with *PAX8PPARgamma* rearrangements are also follicular tumors and would be categorized based on the extent of capsular or vascular invasion (24). Tumors without known mutations or rearrangements can often be categorized on the basis of infiltrative versus encapsulated (circumscribed) pathology.

Although still a work in progress, the reclassification of some FVPTC as NIFTP codifies the mixed but limited nature of FVPTC variants: some resemble cPTC, some resemble FTC, and some resemble follicular adenomas (NIFTP). The prognosis and therapy of these entities clearly requires this distinction. I eagerly await the additional reclassification of FVPTC.

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