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# Implications of the TCGA Genomic Characterization of Papillary Thyroid Carcinoma for Thyroid Pathology: Does Follicular Variant Papillary Thyroid Carcinoma Exist?

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THE HISTORY OF THYROID PATHOLOGY has evolved over many years as pathologists identified characteristic morphologic features of tumors that were associated with distinct clinical behaviors. In the 1960s, thyroid tumor classification was relatively simple. Papillary thyroid carcinoma (PTC) was recognized as a tumor with papillary architecture and as a relatively indolent but locally invasive malignancy that had a predominant tendency to spread to regional lymph nodes. Conversely, follicular thyroid carcinoma (FTC) was a follicular-patterned tumor that was usually expansile and encapsulated but invaded through its capsule and into blood vessels to spread hematogenously; carcinomas with mixed papillary and follicular architectures were determined to behave more like PTCs.

Beginning in the 1970s, endocrine pathologists realized that this simplicity did not capture the full complexity of the situation. Following seminal studies of Lindsay (1), the important recognition in 1977 of the value of nuclear features to predict PTC-like behavior in follicular-patterned tumors gave rise to a new entity: the follicular variant of PTC (FVPTC) (2,3).

In 2014, we face a very complex classification of thyroid carcinomas with multiple variants of every major tumor type (4). As in every field, there are pathologists who are ''splitters'' and subclassify every variant, and there are ''lumpers'' who prefer to consolidate lesions with similar behaviors and only recognize as important those variants that have clinical significance. While every variant of thyroid cancer has its proponents, there comes a point where differences lose their value by complicating the ability to compare data and thus contribute to appropriate patient care.

Molecular classifications of cancers allow pathologists to step back and recognize the biological basis for similarities and differences in the various subtypes of malignancies. The recent publication of an integrated genomic characterization of papillary thyroid carcinoma by The Cancer Genome Atlas (TCGA) Research Network has done exactly that for the most common endocrine malignancy—PTC (5).

One of the most important outcomes of this study is the validation of morphology as a reflection of tumor biology and an important parameter in determining tumor behavior. The classification of PTCs into $BRAF^{V600E}$-like and *RAS*-like tumors with strikingly distinct genomic features has provided validation of the conventional distinction between classical PTCs and FVPTCs. While the former generally fall into the $BRAF^{V600E}$-like category, follicular architecture and relatively subtle nuclear atypia are the hallmark of the *RAS*-like lesions that are classified as FVPTC. The thyroid differentiation scores (TDS) that were determined based on expression of thyroid function genes in this integrated analysis support the clinical evidence that FVPTC displays a gene expression profile that resembles normal thyroid, as we would expect based on its morphology, whereas classical and tall cell PTCs, while still falling within the category of well-differentiated thyroid cancers, are $BRAF^{V600E}$-like and show relatively less evidence of thyroid differentiation with lower expression levels of TDS genes.

What the TCGA findings do not address is the distinction between FVPTC and FTC. Although not specifically included in the analysis, FTCs are known to harbor *RAS* mutations and have frequent copy number changes (6,7). The common detection of the same *RAS* mutations and arm-level copy number changes in FVPTC raises the question as to whether FTC and FVPTC are truly distinct entities and, importantly, whether the distinction is of biologic and clinical relevance. Moreover, it is almost certain that some of the 99 FVPTCs included in the study would have been diagnosed as FTCs by some experts, since this area is the subject of one of the controversial disputes in pathology (8,9). There is essentially no consensus regarding the nuclear features seen in FVPTC, that is, how florid nuclear atypia must be or how many atypical nuclei in a follicular lesion are required to classify a neoplasm as FVPTC. Nevertheless, the fact remains that thyroid tumors that show complete follicular architecture and grow as expansile and often encapsulated masses harbor *RAS* or *RAS*-like mutations as the hallmark of their genetic signature.

Pathologists must now reconsider the value of separating these nearly identical lesions into FTC and FVPTC. We propose that the time has come, based on molecular evidence, to do away with the verbose and often confusing terminology

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''follicular variant of papillary thyroid carcinoma.'' But what will the implications of this reclassification be?

The implications for PTC will be clear—the terminology will remain applicable to all thyroid carcinomas that have any form of papillary architecture (except for the rare benign papillary lesions known as ''papillary hyperplastic nodules'' or ''follicular adenomas with papillary hyperplastic features'' that lack any of the nuclear atypia of PTC and are generally functioning nodules). This classification will be used for all infiltrative lesions, despite follicular architecture that may predominate (10). These $BRAF^{V600E}$-like lesions will be expected to behave like classical or tall-cell PTC. However, beyond this separation, the TCGA study illustrates the genetic heterogeneity present in these ''true'' PTCs that reflects other genetic changes beyond the common driving alterations and/or altered miRNA expression. Much of this genetic heterogeneity is reflected in tumor morphology (e.g., tall cell), and it will require additional validation efforts—morphological and molecular—to establish the best way to uncover these differences in pathology practice. Such work is already underway.

The implications for follicular-patterned lesions and FTC are more onerous. As we recognize that expansile thyroid neoplasms with follicular architecture are all *RAS*-like tumors with high TDS, the distinction between benign, malignant, and aggressive neoplasms remains a challenge. The true predictor of malignant potential in follicular-patterned tumors remains unclear, but may well be one or several of the candidates: nuclear features that were the foundation of FVPTC, the *RAS* gene mutation signature, capsular invasion, angioinvasion, or some combination of these. While as pathologists we have been rewarded with the validation of papillary-patterned PTC by genomics, we remain humbled by our lack of consensus concerning the nuclear atypia and features of these follicular-patterned tumors. We must also admit our limitations in identifying capsular invasion based on sampling of capsular tissue for examination, since no tumor can undergo complete capsular examination using our routine histologic approaches. Even the criteria for assessing angioinvasion are inconsistent and controversial (11), and as with the capsule of these tumors, there is no way to ensure thorough evaluation of every relevant vessel using histology. Those of us following patients who have developed metastatic carcinoma after the diagnosis of follicular adenoma have studied those tumors carefully. While we often can agree retrospectively that there was nuclear atypia and/or evidence of invasion, there is still difficulty in the pathology community accepting those features prospectively in new cases.

The TCGA study provides us with the opportunity to simplify thyroid cancer classification by putting an end to the complexity of FVPTC. Instead, we should refocus our efforts to move forward with meaningful studies of the complex area of follicular thyroid neoplasia. Ideally, large-scale pan-genomic studies like TCGA of benign and malignant follicular tumors will address this problem.



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