



## THYROID CANCER

# Multiple Variants of Noninvasive Follicular Neoplasm with Papillary-like Nuclear Features (NIFTP)

### BACKGROUND

Papillary cancer is the most common type of thyroid cancer. Follicular variant of papillary thyroid carcinoma represents 30% of all papillary thyroid cancers and, like the classic type of papillary cancer, has a good prognosis overall. The follicular variant can be further divided into encapsulated (better prognosis) and invasive (worse prognosis) types. Although encapsulated follicular variant of papillary thyroid carcinoma has a good prognosis overall, further characterization with the absence of certain adverse features on examining these cancers under the microscope has led to another variant termed noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP), which is currently considered to not be a cancer. At present, the diagnosis of NIFTP is a pathologic one, meaning that it can only be diagnosed after surgery with review under a microscope. The goal of this study is to evaluate the molecular profile of NIFTPs in comparison to benign follicular adenomas and the invasive follicular variant of papillary thyroid carcinoma.

### THE FULL ARTICLE TITLE:

Giannini R et al. Identification of two distinct molecular subtypes of non-invasive follicular neoplasm with papillary-like nuclear features by digital RNA counting. *Thyroid* 2017;27:1267-76. Epub September 5, 2017.

### SUMMARY OF THE STUDY:

The study included 62 patients diagnosed with follicular adenomas and follicular variant of papillary thyroid carcinoma who underwent thyroid surgery at the University of Pisa, Italy between 2013 and 2015. The thyroid cancer samples were re-evaluated by two pathologists and reclassified as follicular adenomas, encapsulated follicular variant of papillary thyroid carcinoma and invasive follicular variant of papillary thyroid carcinomas. Among the 30 encapsulated follicular variant of papillary thyroid carcinomas, 26 cases did not have adverse features and were classified as NIFTPs. The study evaluated the differences in the gene expression of 75 genes, most of them involving thyroid hormone synthesis, and for the presence of BRAF and RAS gene mutations in 18

follicular adenomas, 18 invasive follicular variant of papillary thyroid carcinomas and 26 NIFTPs.

Follicular adenomas and invasive follicular variant of papillary thyroid carcinomas had different and distinct gene expression profiles. The 26 NIFTPs showed either follicular adenoma-like gene expression profile (13 cases) or invasive follicular variant of papillary thyroid carcinoma-like gene expression profile (13 cases). A total of 13 NIFTPs showed predominantly RAS but also BRAF mutations, the mutations being more common in NIFTPs with invasive follicular variant of papillary thyroid carcinoma-like gene expression (11 of 11) than in those with follicular adenoma-like gene expression (2 of 13). Most BRAF mutations in NIFTPs were noted at V601 locus, while V600 locus mutations are usually seen in invasive thyroid cancer.

Among the NIFTP tumors with invasive follicular variant of papillary thyroid carcinoma-like gene expression, 5 had a NRAS Q61R gene mutation, 2 had a HRAS Q61R gene mutation, 3 had a BRAF k601E gene mutation and one had a BRAF V600E gene mutation. Among the NIFTP tumors with a follicular adenoma-like gene expression, one had an HRAS Q61R gene mutation and another had an NRAS Q61R gene mutation.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This is the first study that reports the presence of two different gene expression profiles in patients with NIFTP tumors. The NIFTP tumors with follicular variant of papillary thyroid carcinoma-like gene expression showed more frequent RAS and BRAF gene mutations as compared to tumors with follicular adenoma-like gene expression, so these may be precursors of thyroid cancer. Currently, NIFTP tumors need to be removed surgically for diagnosis and this study does not change this. Further studies are needed to define a list of genes that characterize NIFTPs, which could be used to identify these lesions by thyroid biopsy cytology and result in less invasive diagnostic procedures.

— Alina Gavriila, MD, MMSC





## THYROID CANCER, continued

### ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): <https://www.thyroid.org/thyroid-cancer/>

### ABBREVIATIONS & DEFINITIONS

**Papillary thyroid cancer (PTC):** the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

**Follicular variant of papillary thyroid cancer (FVPTC):** one of the subtypes of papillary thyroid carcinoma, which has been classified to two different forms with different prognostic: encapsulated or well-demarcated and invasive.

**Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP):** a new term has been used to describe a type of papillary thyroid cancer which is non-invasive. These cancers behave less aggressively than typical papillary thyroid cancer and have been shown to have low risk for recurrence and low risk for spread outside of the thyroid.

**Follicular Adenoma (FA):** benign (non-cancerous) tumor of the thyroid gland.

**Molecular profile:** genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid specimens to either diagnose cancer or determine that the nodule is benign.

**Mutation:** A permanent change in one of the genes.

**Genes:** a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

**Cancer-associated genes:** these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.

**Thyroid fine needle aspiration biopsy (FNA):** a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

