

Title Page**Non-invasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP): Reducing overtreatment by reclassifying an indolent variant of papillary thyroid cancer****David N Poller, Yuri E Nikiforov**

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Competing Interests

Dr Poller declares no competing interests

Prof. Nikiforov declares that he is a consultant for Quest Diagnostics

Worldwide the rising incidence of cancer is attributed to ageing populations, environmental and lifestyle factors, and increased cancer surveillance. Cancer surveillance leads to increased early detection of indolent cancers and in some cases to cancer '*overdiagnosis*'¹. In the thyroid the increased incidence of thyroid cancer and cancer detection is primarily due to widespread use of thyroid ultrasound². This excess of newly diagnosed thyroid cancers occurs almost entirely because of greater detection papillary thyroid cancers, a tumour which under the microscope shows a characteristic papillary growth pattern together with typical nuclear features. Follicular variant of papillary carcinoma (FVPTC) is one of two major subtypes of papillary thyroid cancer. The encapsulated type of follicular variant of papillary carcinoma (eFVPTC), a tumour which under the microscope shows no invasion of surrounding thyroid, blood vessels, or lymphatics has increased in incidence 2 to 3 times over the last 20 to 30 years. eFVPTC is now estimated to comprise approximately 10 to 20% of all newly diagnosed thyroid cancers in Europe and North America^{3,4}. eFVPTC is challenging to diagnose and controversial because the tumour does not show invasion and so the diagnosis rests entirely on the ability of the pathologist to identify the characteristic papillary nuclear features despite the microscopic features of eFVPTC being very subjective^{5,6,7}. Although eFVPTC thyroid cancers behave in a very indolent fashion patients with eFVPTC are often treated in a similar way to those patients with more aggressive thyroid tumours that show invasion, for example with completion thyroidectomy, that is removal of the whole thyroid gland as a second operation followed by radioiodine for thyroid gland ablation.

In the last few weeks, a large international working group of thyroid pathologists and clinical thyroid experts has published the results of an international collaboration aimed to re-evaluate the pathological criteria and clinical behaviour of eFVPTC. The study shows that the pathological diagnostic criteria for FVPTC can now be standardized. Most importantly, when eFVPTC were diagnosed based on these criteria and the tumours were non-invasive, none of 109 patients followed on average for 14 years developed any adverse events despite the presence of nuclear

features of papillary carcinoma. Based on this outcome, some FVPTC thyroid tumours which until just few months ago would have been diagnosed as '*carcinoma*' should no longer be regarded as '*cancers*' but rather as a tumour with a very low risk of malignancy, designated as '*non-invasive follicular thyroid neoplasm with papillary like nuclei, a NIFTP*'⁸. There are also now a series of other articles on NIFTP exploring the effects on rates of pathological diagnosis of thyroid cancer⁹ and FNA cytology diagnosis^{10,11} of cancer in thyroid nodules and the implications for patients. Pre-operative diagnosis of thyroid nodules using thyroid FNA cytology will change as the positive predictive value (PPV) - the likelihood that a diagnosis of malignancy is indeed a true malignant for a Bethesda Class VI thyroid FNA (in the UK these are termed Thy 5) is predicted to fall from 99% to around 95% with a similar reduction in the PPV for malignancy of Bethesda Class V, IV, and III FNA's, -in the UK these categories are broadly equivalent to Thy 4, Thy 3F and Thy 3A thyroid FNA's. Despite this reclassification, it is important to stress that NIFTP is still a tumour driven by potent oncogenes, such as *RAS*, and has to be surgically excised in order to rule out invasion, which separate these tumours from invasive PTC. Therefore, NIFTP is a surgical disease, but removal by lobectomy should be a curative and these patients will not benefit from completion total thyroidectomy and radioiodine therapy. Cytologists and multi-disciplinary teams will have to adjust their management strategies to accommodate the NIFTP diagnosis.

There are undoubtedly other areas in cancer diagnosis where the terminology '*cancer*' has persisted over time and where terminology change is perhaps required e.g. in the breast for '*lobular in situ neoplasia*' rather than '*lobular carcinoma in situ*'.

This study demonstrates the value of international collaboration in applying evidence based medicine including molecular tumour subtyping to develop new diagnostic thresholds for disease, including cancers, in response to increased cancer incidence due to the worldwide ageing of

populations in developed countries and increased public awareness and demand for both appropriate and cost effective healthcare.

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