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Effect of Lowering the Diagnostic Threshold for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma on the Prevalence of Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features: A Single-institution Experience in Korea

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Abstract

The incidence of follicular variant of papillary thyroid carcinoma (FVPTC) has increased to 20% to 30% of all papillary thyroid carcinomas (PTC) over the last three decades in the USA. Non-invasive encapsulated FVPTC comprises of half to two-thirds of all FVPTCs, and is now reclassified as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Asian populations were found to have a lower incidence of NIFTP than the Western populations. In our institution, the incidence of NIFTP for the time period of 2008-2011 was 0.3% (95% confidence interval: 0.1% - 0.5%) of all PTCs, whereas it showed a much higher rate of 3.4% during the period of 2012 to 2014 (95% confidence interval: 2.7% - 4.1%) ($P < 0.0001$). The rising incidence of NIFTP in recent years is mainly attributed to the lowering diagnostic threshold for PTC-type nuclear features in encapsulated follicular tumors. However, despite the increased incidence of NIFTP in our institution, the rate was still 3-6 times less than the 15-25% prevalence reported in the Western series. We discuss implications of this paradigm shift on the prevalence, diagnosis and treatment of thyroid cancers in Korea.

Keywords: Thyroid neoplasm, papillary carcinoma, non-invasive follicular thyroid neoplasm with papillary-like nuclear features, prevalence

Introduction

For a long time, nuclear features of the follicular cells have been considered as the gold standard for diagnosing papillary thyroid carcinoma (PTC). Architectural patterns, such as tumor growth patterns (e.g., papillary, follicular, or solid growth patterns) and demonstration of a capsular or vascular invasion, have not been required to render a diagnosis of PTC. The follicular variant of PTC (FVPTC) is the most common subtype and is predominantly composed of follicles with characteristic PTC-type nuclear features and no true papillae. FVPTC is divided into two main subtypes, infiltrative and encapsulated, based on morphologic features and clinical behavior. Infiltrative FVPTC has an infiltrative tumor border, while the border of encapsulated FVPTC is typically pushing with a fibrous capsule. In terms of clinical behavior, infiltrative FVPTC is similar to classic PTC, whereas the encapsulated FVPTC confers more favorable clinical outcomes than do infiltrative thyroid tumors. The encapsulated FVPTC is further subdivided into invasive and non-invasive forms based on a capsular or vascular invasion (Figure 1). Non-invasive encapsulated FVPTC has an excellent prognosis and behaves like benign follicular adenoma (1). Encapsulated FVPTC, regardless of invasion status, exhibits molecular features characterized by frequent *RAS* mutations and *PAX8-PPARγ* rearrangement, and no *BRAF V600E* mutation, which is more like those of follicular adenoma and follicular carcinoma, rather than those of infiltrative FVPTC and classic PTC (2, 3). An international group of experts has recently renamed the non-invasive encapsulated FVPTC as "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) (2).

The upcoming fourth edition of the World Health Organization (WHO) Classification of Tumors of the Thyroid Gland has adopted the new nomenclature, NIFTP, which was formerly known as non-invasive encapsulated FVPTC (2). In the 2017 WHO classification, the two main subtypes of FVPTC are infiltrative FVPTC and invasive encapsulated FVPTC. NIFTP is no longer considered a subtype of PTC. Other rare subtypes of FVPTC are macrofollicular variant and diffuse or multinodular FVPTC. NIFTP encompasses encapsulated or well circumscribed follicular tumors with incompletely developed, questionable nuclear features of PTC and no papillae, as well as non-invasive encapsulated FVPTC. NIFTP has strict diagnostic criteria established by an international Endocrine Pathology Society working group (2). The histologic features not seen in the NIFTP are >1% of true papillae, psammoma bodies, tumor necrosis, high mitotic activity (≥3 per 10 high-power fields), >30% of solid/trabecular/insular growth pattern, and a capsular or vascular invasion (2). Tumors with these features can be classified as other variants of PTC or poorly differentiated thyroid carcinoma. NIFTP can be totally encapsulated with a thick or thin capsule, or partially encapsulated or well circumscribed with no capsule but it must be clearly demarcated from the adjacent non-tumor tissue. It is important to submit all the entire capsule, adjacent tissue interface of the encapsulated lesions, as well as the tumor tissue to evaluate histologic inclusion/exclusion criteria.

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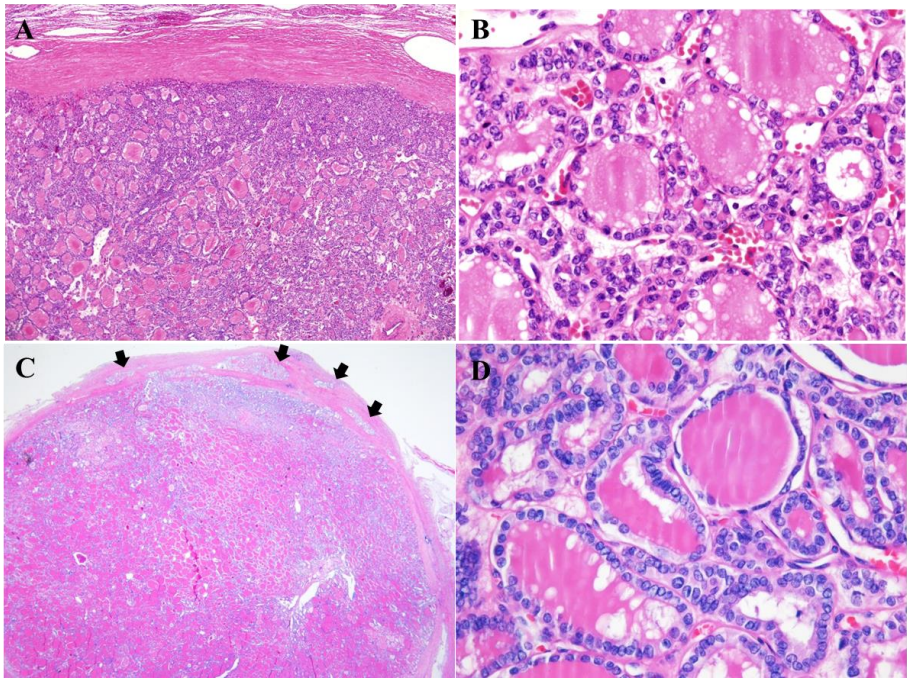

Fig. 1. Encapsulated follicular variant of papillary thyroid carcinoma. Non-invasive encapsulated follicular variant (A and B) is now reclassified as follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). A. The tumor is composed of a mixture of micro- and macro-follicles and has a fibrous capsule (x40). B. The nuclei of tumor cells are enlarged, crowded, and overlapping. They exhibit irregular nuclear contours, grooves and chromatin clearing (x400). C. Invasive encapsulated follicular variant shows a capsular and/or vascular invasion (arrows) (x12.5). D. The tumor cells show papillary carcinoma-like nuclear features (x400).

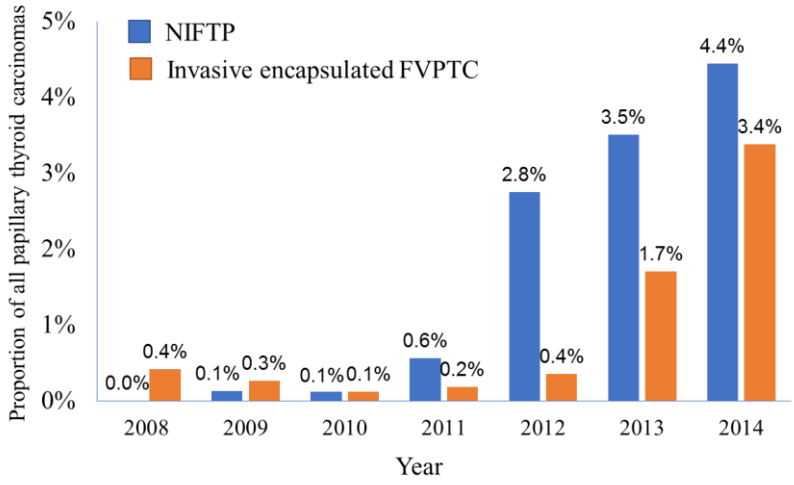

Fig. 2. Incidence of follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and invasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC) at Seoul St. Mary's Hospital, 2008 - 2014.

Trends in the prevalence of FVPTC in the USA

The diagnostic threshold of PTC-type nuclear features varies greatly among pathologists. As a consequence, there is a low interobserver concordance in the diagnosis of encapsulated FVPTC (4). The lowering of the diagnostic threshold of nuclear features of PTC has been attributed to the increase of the prevalence of FVPTC, and possibly to the decreasing rate of diagnosed follicular carcinoma (5). Ratios of PTC-to-follicular carcinoma incidence steadily increased over time in the analyses of the Surveillance, Epidemiology, and End Results (SEER)'s 9-Registry Database (1980-2009) in the USA (6). FVPTC comprises of 20% to 30% of all PTCs in the USA (7), of which encapsulated FVPTCs accounts for half to two-thirds of all FVPTCs (8, 9). Now, the estimated mean incidence rate of non-invasive encapsulated FVPTC is 18.6% of all PTCs based on American and Italian studies (2).

A single-institution experience of the diagnosis of encapsulated FVPTC and NIFTP

Strict criteria suggested by Dr. Chan had been widely used to diagnose an encapsulated FVPTC until around 2010 in Korea (10). Encapsulated follicular tumors showing questionable nuclear features of PTC were mostly diagnosed as follicular adenoma, nodular hyperplasia, or well differentiated tumor of uncertain malignant potential.

One pathologist (CKJ) among the authors had the chance to do research on thyroid tumors at the Dr. Nikiforov Research Lab at the University of Pittsburgh from 2010 to 2011 (11). During that time, the pathologist realized that there was a significant paradigm shift in how encapsulated FVPTC was diagnosed. Most USA pathologists used much less strict criteria to diagnose encapsulated FVPTC than did Korean pathologists at that time. After the pathologist returned to Seoul St Mary's Hospital in December 2011, the "loose diagnostic criteria" were adopted to define encapsulated FVPTC since 2012. After the adoption, even when nuclear features were not well developed and focally present, the encapsulated follicular tumors were more likely to be diagnosed as encapsulated FVPTC. Among the major nuclear features seen in classic PTC, the more important features were nuclear enlargement/overlapping and irregular nuclear contours in our diagnostic criteria. When the nuclear changes were multifocal but not diffuse, the entire tumor was considered malignant. In our retrospective review of around 6,200 PTCs at Seoul St. Mary's Hospital (in press), the overall proportions of invasive encapsulated FVPTC and NIFTP significantly increased after 2011 ($P_{trend} < 0.0001$) (Figure 2). From 2012 to 2014, NIFTP constituted 3.4% (95% confidence interval: 2.7% - 4.1%) of all PTCs as compared with 0.3% (95% confidence interval: 0.1% - 0.5%) in the time period of 2008 - 2011 ($P < 0.0001$). Despite the rise in the incidence of NIFTP at Seoul St. Mary's Hospital, the rate was still 3-6 times less compared to the 15-25% incidence of Western PTC series (2, 12-15). Even before the paradigm shift in the NIFTP, we considered non-invasive encapsulated FVPTC as a very low risk cancer that can be treated with lobectomy alone and no further treatment after surgery, other than the nomenclature change.

Conclusion

In our data, the increased incidence of NIFTP and invasive encapsulated FVPTC may be due to the lowering diagnostic threshold for PTC-type nuclear features in encapsulated follicular tumors. Despite rising incidence of NIFTP in recent years, we expect only a minor impact of NIFTP on the problem of overdiagnosis and overtreatment of thyroid cancers in Korea.

Conflict of Interest: None

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