EDITORIAL

Noninvasive Encapsulated Follicular Variant of Papillary Thyroid "Cancer" (or Not)
Time for a Name Change

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Many subtypes of papillary thyroid cancer (PTC) have been described, of which classic PTC is the most common (70%-80%). The follicular variant of PTC (FVPTC) is the second most common subtype. It has increased in incidence by 4-fold in the last 3 decades, now making up approximately 20% of all thyroid cancers in Europe and North America.[1,2]

The follicular variant of FVPTC presents several diagnostic and management challenges. Most FVPTCs are encapsulated tumors, which are cytologically difficult to distinguish from benign follicular lesions such as follicular adenoma. Several studies highlight this by demonstrating the considerable interobserver variability involved with the diagnosis of FVPTC.[3,4] Multiple studies have shown that encapsulated FVPTCs (EFVPTCs) rarely exhibit lymph node metastases and most behave like a follicular adenoma. Several key retrospective studies have previously demonstrated that the noninvasive EFVPTC (no vascular or capsular invasion) is a highly indolent tumor demonstrating a risk of recurrence of less than 1% in more than 300 previously published cases with extended follow-up, despite the fact that for the majority, treatment consisted of lobectomy only, without radioiodine (RAI) ablation.[5-13] On a molecular level, oncogenic mutations present in noninvasive EFVPTC are similar to follicular adenoma, with a high rate of *RAS* mutations and no *BRAF* mutations.[7]

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The management of noninvasive EFVPTC should depend on the biologic behavior of the tumor. The recent American Thyroid Association[14] guidelines recommend careful risk stratification and advocate for a more measured and risk-adapted approach to both diagnosis and treatment of thyroid cancer. The extent of surgery (partial vs total thyroidectomy), role of completion thyroidectomy, central neck dissection, and postoperative RAI treatment to help prevent recurrent disease are all dependent on the malignant potential of the primary tumor. Despite this, noninvasive EFVPTCs are often overtreated, leading to increased potential morbidity, emotional and psychological stress, and increased financial burden and health care costs.

For this reason, Nikiforov et al[15] have published a timely article calling for nomenclature revision for EFVPTCs. The authors participated in the Endocrine Pathology Society's conference to reevaluate noninvasive EFVPTC in Boston, Massachusetts, in March 2015. Through a number of premeeting conference calls and then a 2-day in-person meeting, the conclusion of this group was to rename these tumors *noninvasive follicular thyroid neoplasm with papillary-like nuclear features* (NIFTP).

This international multidisciplinary panel of experts analyzed a group of more than 200 EFVPTC cases. They compared 109 noninvasive EFVPTC cases with 101 invasive EFVPTC cases. Tumors were reviewed by 24 expert pathologists in 7 different countries. Despite prevalent management with lobectomy without RAI treatment, no evidence of recurrence or disease-related death occurred in the noninvasive EFVPTC cohort of patients observed for 10 to 26 years. Concordant with multiple previous studies, genetic analysis of these lesions also demonstrated that noninvasive EFVPTC is predominantly driven by *RAS* mutation typically associated with follicular lesions, as opposed to *BRAF* and *RET* rearrangements, which have been associated with classic PTC. On the basis of this and a thorough review of the literature, the authors recommend a name change for noninvasive EFVPTC to NIFTP. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features is characterized by (1) encapsulation or clear demarcation of the tumor from adjacent thyroid tissue with no invasion, (2) a follicular growth pattern, and (3) at least moderately expressed nuclear features of papillary carcinoma. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features, driven by *RAS* and *RAS*-like mutations, represents a preinvasive stage of invasive encapsulated follicular variant papillary carcinoma. Furthermore, the authors provide a simplified diagnostic nuclear scoring system with stringent criteria that could be used to successfully reproduce and accurately identify the histologic diagnosis of NIFTP.

The results of this study, together with previously reported observations, suggest that when the diagnosis of NIFTP is made on the basis of careful histopathological examination, the tumor will have a low recurrence rate, likely less than 1% within the first 15 years. This carries important implications, given that EFVPTC accounts for 20% of thyroid cancer. The change in nomenclature could affect the clinical care and management of more than 45 000 patients worldwide per year.[15]

By removing the word *cancer*, the term *NIFTP* acknowledges the low malignant potential of these tumors. This will potentially affect the way the disease is viewed by caregivers and patients. It will eliminate the psychological impact of receiving a cancer diagnosis. Furthermore, the new designation recognizes the appropriate biological behavior of this tumor and

should decrease the overtreatment that the term *cancer* often breeds. The inevitable financial repercussions associated with this change are critical for our health care system.

Recent studies have demonstrated that patients with cancer were 2.65 times more likely to file for bankruptcy than people without cancer. Younger patients with cancer had 2 to 5 times higher rates of bankruptcy than patients with cancer aged 65 years or older. Patients with thyroid cancer had the highest overall incidence of bankruptcy at 1 year after diagnosis, per 1000 person-years.[16] Renaming noninvasive EFVPTC to NIFTP will likely mitigate the financial burden for these patients. It is also likely to result in overall health care cost savings and reductions by obviating completion thyroidectomy and RAI treatment, both of which are also associated with complications such as recurrent laryngeal nerve injury, superior laryngeal nerve injury, hypoparathyroidism, and secondary malignant neoplasms.[17,18] Significant cost savings could also result from decreasing long-term surveillance with reduced office visits, as well as unnecessary ancillary radiographic and biochemical testing.

The reclassification of noninvasive EFVPTC to NIFTP is a timely and appropriate change. It highlights the true biologic nature of this tumor, lessens the emotional and psychological burden associated with the term *cancer*, and results in increased cost savings by potentially decreasing overtreatment that exposes patients to unnecessary risks.

ARTICLE INFORMATION

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