Journal of Basic & Clinical Medicine

http://www.sspublications.org/index.php/JBCM/index

Coming to Terms with Diagnosis "Non-Invasive Follicular Neoplasm with Papillary Like Nuclear Features (NIFTP)': Practice Changer in Endocrine Pathology

Virginia A. LiVolsi* and Zubair W. Baloch

Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Journal of Basic & Clinical Medicine 2017; 6(1):8-13

Abstract

This review summarizes the history and development of the concept of noninvasive follicular thyroid tumor with papillary like nuclear features (NIFTP). The salient histopathologic features of this lesion are discussed with emphasis on inclusion and exclusion criteria in light of available data. Immunohistochemical and molecular profiles are presented. The authors also provide their own point of view regarding the practical issues and concerns that are known to surface based on the diagnosis of NIFTP. This discussion also includes the re-review of lesions that once were classified as carcinoma.

Keywords: Thyroid, follicular thyroid carcinoma, papillary thyroid carcinoma, non-invasive carcinoma, NIFTP

Describing Present and Future in View of the Past

Prior to the 1960s, the distinction between papillary and follicular thyroid carcinoma was predicated on the percentage of follicular pattern of growth. Thus the Armed Forces Institute of Pathology fascicle indicated that, if a thyroid tumor showed greater than 50% follicular pattern, it should be diagnosed as "follicular thyroid carcinoma", and those lesions with more than 50% papillary pattern were "papillary carcinoma" (1, 2).

Beginning in the 1960s with the suggestion that nuclear features predicted biological behavior in follicular patterned thyroid tumors, the concept of the follicular variant of papillary carcinoma arose. In 1977, Chen and Rosai named these lesions, but the seven cases they reported were all infiltrative neoplasms (3). Such neoplasms recapitulated the biological behavior of classic papillary carcinoma with "multifocal" lesions in the thyroid, lymphatic invasion in the gland and extra thyroidal soft tissue and proclivity for regional lymph node metastases. Distant metastases were quite rare.

Over the last quarter of the 20th century and into the 1st decade of the 21st century, lesions which were encapsulated, follicular patterned but with papillary cancer nuclei were recognized and diagnosed as "follicular variant of papillary carcinoma". When invasive, such lesions however followed a clinical pathway resembling follicular carcinoma since when there was invasion of these lesions either of the tumor capsule or vessels within the tumor capsule or in the adjacent thyroid parenchyma, hematogenous metastasis to bones and brain were common. Nodal metastases were unusual. However, when there was no invasion in a well sampled and studied lesional capsule and if there were no papillae (hybrid of papillary and follicular growth patterns) or psammoma bodies, such lesions appeared on follow-up to behave in a benign fashion, follicular adenoma or follicular patterned adenomatoid nodule. Studies published from Europe, Asia and the United Stated segregated those encapsulated lesions with no invasion from those with invasion and indicated the former group were indolent lesions clinically (4-6). Hence it appeared that there exist two major categories of follicular variant of papillary carcinoma - the infiltrative type and the encapsulated type.

Problems arose in the diagnosis of follicular variant of papillary thyroid carcinoma-encapsulated type since even the "experts" in endocrine pathology showed very poor agreement among themselves in defining the diagnostic nuclear features of papillary carcinoma (7-12). The study by Lloyd *et al*. evaluating the interobserver variability showed that a concordant diagnosis of follicular variant of papillary thyroid carcinoma was made by all ten reviewers with a cumulative frequency of only 39% (7). An interesting study by Hirokawa *et al*. of the encapsulated follicular patterned thyroid lesions examined by four American and four Japanese pathologists showed unanimous agreement among all pathologists in two (10%) cases. Interestingly, the American pathologists frequently made the diagnosis follicular variant of papillary thyroid carcinoma as compared to Japanese pathologists (25% *vs*. 4%) (8). Thus, most experts agreed that this variability in the diagnosis of follicular variant of papillary thyroid carcinoma is due to the lack of agreement on the minimal diagnostic criteria (7, 12). As afore-mentioned, the diagnosis of papillary cancer is made by examining the tumor cell nuclei. Most cytopathologists will not render the diagnosis of papillary carcinoma in thyroid fine needle aspiration (FNA) specimens until all major diagnostic features are readily identifiable. Most FNA specimens that lacked one or more of major-diagnostic criteria were classified as suspicious for papillary thyroid carcinoma (13, 14). Numerous studies from various academic and non-academic centers have shown that the rate of malignancy in cases diagnosed as such is 60-75% and interestingly, most cases on histologic examination are found to be follicular variant of papillary thyroid carcinoma (14, 15).

These above-mentioned studies attest to the fact that there is significant inter- and intra-observer variability in the diagnosis of follicular variant of papillary thyroid carcinoma, which often created treatment dilemmas among clinicians, i.e. whether to treat or not, i.e. completion thyroidectomy (in cases where lobectomy is done as the initial procedure) and/or radioactive iodine ablation.

Received: January 17, 2017; Accepted: January 29, 2017
*Correspondence author: Dr. Virginia A. LiVolsi, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania Medical Center; 6 Founders Pavilion, 3400 Spruce Street, Philadelphia, PA 19104. Tel: 215-662-6544; Fax: 215-662-6545;
Email: linus@mail.med.upenn.edu

The result of this diagnostic conundrum was that many cases of follicular variant of papillary thyroid (especially encapsulated lesions) were sent to thyroid pathology experts for second opinion (9, 16). In light of this controversy, the "Chernobyl Pathology Panel" was the first to recommend the encapsulated follicular variant of papillary thyroid carcinoma be termed as "well-differentiated thyroid tumor of uncertain malignant potential" (4).

Molecular Studies and Clinical Follow-up Pave the Way

The elegant molecular studies of almost 500 cases of papillary carcinoma and its variants under the National Cancer Institute supported "The Cancer Genome Atlas (TCGA)" showed that the two subtypes of papillary thyroid carcinoma, the conventional/classic and follicular variants, were different also at the molecular level. Hence papillary carcinoma and its variants that maintained papillary growth pattern (tall cell, columnar cell, diffuse sclerosis variant, among others) or that had infiltrative growth demonstrated mutations in BRAF V600E or translocations (rearrangements) in RET (17, 18). On the other hand, follicular patterned tumors that were encapsulated showed molecular signatures similar to those of follicular adenomas/carcinomas, i.e. mutations in the RAS pathway (17, 19, 20). This major discovery finally could make sense and correlate with studies from various laboratories around the world, which showed that the biologic behavior on long term follow-up of these encapsulated noninvasive examples of "the follicular variant of papillary carcinoma" did not recur (or only rarely did) nor spread outside of the thyroid (21, 22). This concept of "low-risk tumors" was further supported by the management strategies put forth by the American Thyroid Association and various endocrine societies around the world for low, intermediate and high risk neoplasms of the thyroid (23).

The Concept and Deliberations

In 2015, an international group of endocrine pathologists, molecular pathologists and clinicians studied a large number of these encapsulated neoplasms with papillary carcinoma nuclei and showed that, if there was no invasion, these lesions carried very low risk to the patient even when treated conservatively as with solely thyroid lobectomy. However, when there was invasion and especially vascular invasion at relatively short follow-up intervals, these tumors behaved aggressively with hematogenous metastasis. Lymph node metastases in the cervical region were rare (in those thyroids harboring noninvasive encapsulated follicular variant of papillary thyroid carcinoma, there often was evidence of separate papillary microcarcinoma or multiple microcarcinomas, suggesting that these latter lesions and not the encapsulated neoplasm represented the primaries for the lymph node metastases).

In thyroid glands in which the only nodule was a noninvasive encapsulated follicular tumor, the biological behavior was so low risk that it seemed inappropriate to label these tumors as "carcinoma". The panel recognized the "toxic" nature of the word "carcinoma" or "cancer", and referenced psychiatric studies that highlighted the stress induced in patients and families when this diagnostic term is used (24). In addition, the effect on insurance premiums for the patients was also noted (25). A variety of diagnostic terms had been suggested in the literature for these encapsulated lesions: "atypical adenoma" (26, 27), "borderline lesion" (28), and tumors of uncertain malignant potential (4)". None of these terms had "caught on" either because patients or their treating physicians felt that all elicited "uncertainty of behavior".

Thus the international panel after long discussion and multiple candidate nomenclatures developed the diagnostic term "noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)" (29). This term, although probably grammatically not sound, avoids the words "carcinoma", "cancer", "malignant" and "uncertain", and applies to these tumors a definitive clinicopathologic designation. It stresses the features of the lesion, i.e. "noninvasive", "follicular", "neoplasm", and gives attribution to the nuclei. It is important to include the "nuclear cytology" in NIFTP, because still on FNA some of these will show atypical nuclear features suggestive or suspicious for papillary thyroid carcinoma. Studies have shown that majority of these will be diagnosed on FNA as atypia/follicular lesion of undetermined significance, follicular neoplasm, and suspicious for papillary thyroid carcinoma.

What's in the Name?

The descriptive terms of **NIFTP** "fit" the lesion.

"*Noninvasive*": Many of these lesions are encapsulated (Figure 1A) but some are not and are only circumscribed. The histologic feature of no invasion is critical for the diagnosis. Invasion of the capsule may be focal; in non-encapsulated tumors, spread or infiltration of neoplastic follicles into the surrounding thyroid may be subtle and some have recommended immunostaining with HBME-1 as a marker to highlight these invasive follicles (Seethala personal communication). The importance of the noninvasive description is paramount and hence requires histological examination of the entire capsule or the entire lesional edge at the tumor and surrounding thyroid parenchyma interface in order to assure an accurate diagnosis.

Additionally, since most of these nodules have been biopsied (either FNA or core biopsy), it is extremely important to distinguish needle biopsy tracts from true tumor capsule invasion. Helpful hints include the geographic (linear) nature of the needle tract, and the association with inflammation and hemosiderin (30, 31).

"*Follicular*": The growth pattern of the lesion is predominantly or exclusively follicular (Figure 1B). The majority of examples show a diffuse or multifocal "microfollicular" growth. Some lesions show admixtures of macrofollicles as well. Often, the microfollicles are found interspersed among the macrofollicles and contain atypical nuclei. Although areas of solid growth are permissible, the panel felt that this should not exceed 30% of the lesion; in such cases careful evaluation for necrosis and mitotic figures should be given so as to rule out a poorly differentiated carcinoma. In addition, no papillary pattern should be allowed (the criteria allow for less than 1% papillae); as a corollary, no psammoma bodies (the ghosts of dead papillae) should be found (29).

"*Neoplasm*": These lesions are neoplasms. The preliminary data of molecular analysis suggest that these are clonal neoplasms often harboring mutations in RAS gene, often the NRAS (29, 32). They do not represent hyperplastic or adenomatous nodules; as well, they are often encapsulated, hypercellular and monotonous in their cellular composition histologically.

"*Papillary like nuclear features*": The distinction of these tumors from follicular adenoma is the presence of nuclear features of papillary carcinoma (Figures 1C and 1D). The original evaluation of these tumors included an elaborate nine-point grading scheme (subsequently reduced to three grades), which assessed the following nuclear parameters: shape and size, membrane irregularities and chromatin features (29).

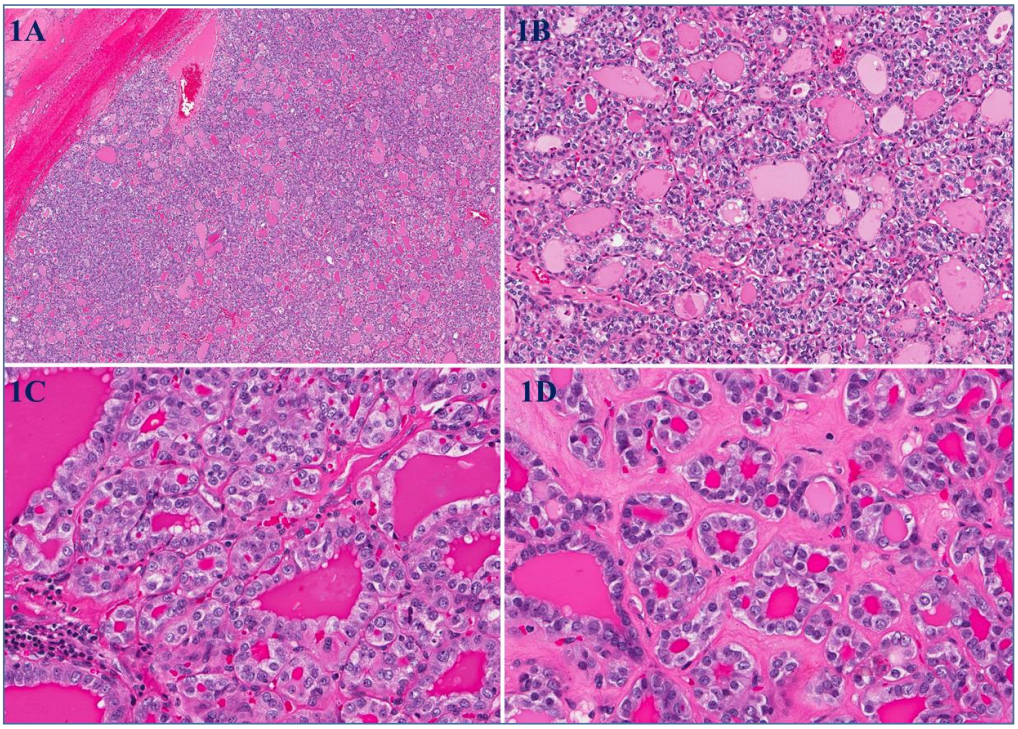

Fig. 1: A case of noninvasive follicular neoplasm with papillary like nuclear features (NIFTP). Low power showing a follicular patterned lesion well demarcated at its periphery (1A, 10x), the medium power showing a mixed pattern consisting of small and medium size follicles some with thick eosinophilic colloid (1B, 20x), and the high power showing follicles lined by cells with atypical nuclear cytology (cytologic features of papillary thyroid carcinoma) (1C and 1D, 40x). Hematoxylin and eosin stain.

The nuclear features can be diffuse or multifocal and can show gradations of nuclear parameters in different areas of the lesion. As with invasive encapsulated tumors or infiltrative varieties, the nuclei show most of the features of those in classic papillary carcinoma except that intranuclear inclusions are rare and the nuclei often are more rounded than oval.

Immunostains: Special stains for various markers (CK19, Galectin 3) as with most papillary carcinomas are not often helpful (29). However, HBME-1 does show membrane staining in about 60-70% of these lesions. The staining may be focal, and in our experience tends to be concentrated in the areas of microfollicular growth (33).

Molecular analysis: Nikiforov *et al*. have shown that those lesions that have been studied may harbor mutations in RAS - 30%, and PPARG or THADA gene fusions - 44%, and only one case showed BRAF K601E mutation (29). In comparison to invasive lesions especially those with vascular invasion, none of the NIFTP cases shows TERT or p53 mutations (29).

The Buck Doesn't Stop Here: Future Directions

Micro-NIFTP: The original description of NIFTP included only lesions that measured greater than 1.0 cm or more. Tumors with the appropriate histological characteristics that measure 1.0 cm or less and thus would be microcarcinomas have not been studied in a systematic fashion. Thompson's series however did include sub-centimeter tumors (smallest was 7 mm) and these seemed to behave in a similar fashion to larger NIFTPs (34). However, until additional data are available for these small tumors, it is recommended that they are diagnosed as "follicular variant of papillary microcarcinoma".

An additional observation about size of NIFTP is appropriate. In the original series, lesions up to 9.0 cm were encountered and in Thompson's data one lesion measured 9.5 cm (29, 34). It has been our experience that, although large nodules can represent NIFTP, in many tumors over 4 cm careful histological assessment of the periphery will show foci of invasion thereby indicating the diagnosis of carcinoma. We have identified two recent cases summarized below:

1. 54-year-old woman with 4.5 cm nodule. Originally 8 sections of edge - no invasion was seen (had papillary carcinoma nuclei). Submitted additional -24 sections of which 5 had capsular and transcapsular invasion. Hence this was encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC with invasion (per criteria "Cancer")).

2. 49-year-old man with 6.9 cm nodule. Original 13 sections of lesional edge - no invasion was seen (showed papillary cancer nuclei). Submitted -49 additional sections of which 4 had capsular and transcapsular invasion; hence this was diagnosed as EFVPTC with foci of tumor capsule invasion and invasion into surrounding thyroid (per criteria "Cancer").

In addition, careful histologic examination of the entire lesion may show a focus or tiny foci of papillary growth and despite the absence of invasion, such lesions rarely can metastasize to regional lymph nodes. We have identified such a case:

1. 32-year-old woman with a 2.7 cm circumscribed nodule shows no invasion but one 1.3 mm focus of papillary growth. A micrometastasis to a peri-isthmic lymph node was identified; hence this was an encapsulated papillary carcinoma.

NIFTP with oncocytic cytology: The presence of foci of or diffuse oncocytic cytology in NIFTP has not been recognized or studied. Since such cytoplasmic change is not uncommon in

infiltrative follicular variant of papillary carcinoma, it seems that some NIFTP may show this alteration. Again, no data are available on this feature and this awaits further studies.

Multifocal lesions in same gland: Some thyroid glands may contain more than one NIFTP (up to 20% in one series) (34). If so, each needs to be fully examined and the diagnosis confirmed. Each should carry the prognosis of one individual tumor. These cases are interesting as they appear to recapitulate "multifocal" classic papillary carcinomas or papillary microcarcinomas. However, some multifocal papillary carcinomas may represent intrathyroidal lymphatic spread of one tumor, which cannot be true for NIFTP as the latter does not show lymphatic invasion. Molecular analysis of these unusual multifocal cases should clarify if these NIFTPs are indeed independent clonal proliferations.

Prognosis and treatment: Based on the available data, one can easily deduce that the great majority of NIFTPs are of low risk and conservative surgical excision is adequate treatment. The evidence so far published indicates that those lesions that are adequately examined microscopically do not recur or metastasize;, possible rare exceptions may exist. The one case published by Baloch *et al*. did not have complete examination of the lesional capsule and bone metastases developed (35). Vivero *et al*. showed a subsequent recurrence of a case in which the initial lesion was transected preventing the complete evaluation of the tumor periphery for invasive characteristics and subsequently recurred (21).

The case of nodal metastasis described by Valderobano *et al*. shows that NIFTP has very low but real malignant potential (platform presentation at American Thyroid Association Annual Meeting, Sept. 2016). This was identified in a retrospective case review; it is unclear how adequately the lesional edge was sampled and examined (36).

Treatment: Treatment for NIFTP is simple lobectomy. In some cases, the thyroid will contain multiple nodules in the opposite lobe or patients who are severely hypothyroid on thyroid replacement therapy and near total or total thyroidectomy is deemed appropriate. When the excised lesion is diagnosed as NIFTP, no further surgery is needed. No postoperative radioactive iodine treatment should be given.

Preoperative diagnosis: The preoperative diagnosis of NIFTP is not possible with our current available modalities. The cytologic diagnosis of this entity has been studied in retrospective analyses (37-41). Most of the lesions are diagnosed on aspiration biopsy as "atypia of undetermined significance", "follicular lesion of undetermined significance", "follicular neoplasm", or "suspicious for papillary carcinoma". A few have been called "malignant-papillary carcinoma". These diagnostic categories reflect the vagaries of the nuclear changes in the category of NIFTP lesions. (Please see also paper on Cytology in another area of this journal).

What NIFTP Is and What It Is Not: Personal View and Cautionary Note

From studies of this lesion, we can claim it is a neoplastic proliferation of thyroid follicular epithelial cells. As noted above, molecular analysis has shown that these are clonal proliferations and share mutational signatures with the family of follicular tumors (follicular adenoma/carcinoma) (18, 20). We also know by follow-up data (clinical, biochemical and radiologic) that these lesions pose very low risk to the patient after their simple but complete removal (6).

What NIFTP is not includes a list of other lesions: papillary carcinoma, encapsulated; follicular variant of papillary carcinoma with invasion; solid papillary carcinoma; poorly differentiated thyroid carcinoma; and follicular adenoma.

The major question is in our view: ***Is NIFTP carcinoma***? We applaud the report by the NIH committee to reassess low grade lesions of various organs which pose minimal risk to patient survival and yet by diagnosing them as "cancer", aggressive and unnecessary treatment is given; "the treatment may be worse than the disease" (25). Hence the committee recommended altered terminology for these low risk lesions, avoiding the "carcinoma" word and replacing it with less "toxic" verbiage.

With that approach in mind, we concur with newer diagnostic terms like indolent lesions of epithelial origin (IDLE) in the prostate (25, 42) or NIFTP in the thyroid. However, we believe NIFTP is equivalent to ductal carcinoma in situ of the breast, or carcinoma in situ of the urinary bladder; that is, it is carcinoma that has not obtained the capacity to invade. The panel did not consider diagnosing these lesions as thyroid carcinoma in situ, as to avoid the toxic rubric of "carcinoma" or "cancer". We believe that, although the risk of recurrence or spread is very low, longer follow-up of well-studied cases is needed. The reportedly rare finding of nodal metastases in women with ductal carcinoma in situ has been correlated with early minimal invasion beyond basement membrane of ducts at the ultrastructual level (43, 44). Hence it is theoretically possible that some similar mechanisms may rarely occur in thyroid encapsulated lesions.

We, however, do not consider NIFTP as equivalent to IDLE (25, 42) in the prostate since those lesions are low-grade but already invasive carcinomas and despite being invasive are associated with excellent prognosis and rare metastatic disease (42).

Should We Go Back? The Dilemma of Retrospective Re-review

The question of reevaluation of slides of nodules removed years before the concept of NIFTP was introduced is a difficult one to answer (45). When the diagnosis of "encapsulated follicular variant of papillary carcinoma" was rendered on these lesions, it was standard of care at that time, also standard was how these were treated.

It is not possible to know in each case how adequately the lesion was pathologically examined and to review the available slides may lead to spurious re-diagnosis. Hence it may be ethically inappropriate to "go back" and reassure the patient of a low risk diagnosis from review of incomplete data. NIFTP is a prospective diagnosis and should remain so.

If the future studies indicate that NIFTP harbors a ***SPECIFIC*** molecular signature that can distinguish it from all papillary carcinomas and can be assayed on existing tissue blocks; then and only then should the diagnosis be changed from carcinoma to NIFTP. However, this is not a reversal of a diagnosis based solely on histopathological review.

Conclusions

This paper reviews "non-invasive follicular variant of papillary thyroid carcinoma" now known as "NIFTP" in view of historical perspective; the features of this lesion and the necessity of careful histopathologic evaluation are stressed. The

immunohistochemistry and molecular characteristics so far known are discussed as well. Finally, the ethical issue of retrospective diagnosis of such lesions is briefly discussed and the authors provide their opinion on this controversial topic.

References

1. Meissner W, Warren S. Tumors of the thyroid gland. 2nd Series, Vol Fascicle 4, 1969. Armed Forces Institute of Pathology, Washington, DC.
2. Warren S, Meissner WA. Tumors of Thyroid Gland. 1st Series, Section IV, Vol Fascicle 14, 1953. Armed Forces Institute of Pathology, Washington, DC.
3. Chen KTC, Rosai J. Follicular variant of thyroid papillary carcinoma: a clinicopathologic study of six cases. Am J Surg Pathol 1977; 1:123-30.
4. Williams ED, Abrosimov A, Bogdanova TI, Rosai J, Sidorov Y, Thomas GA. Two proposals regarding the terminology of thyroid tumors. Guest Editorial. Int J Surg Pathol 2000; 8:181-3.
5. Kakudo K, Bai Y, Liu Z, Ozaki T. Encapsulated papillary thyroid carcinoma, follicular variant: a misnomer. Pathol Int 2012; 62:155-60.
6. Liu J, Singh B, Tallini G, Carlson DL, Katabi N, Shaha A, Tuttle RM, Ghossein RA. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer 2006; 107:1255-64.
7. Lloyd RV, Erickson LA, Casey MB, Lam KY, Lohse CM, Asa SL, Chan JK, DeLellis RA, Harach HR, Kakudo K, LiVolsi VA, Rosai J, Sebo TJ, Sobrinho-Simoes M, Wenig BM, Lae ME. Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. Am J Surg Pathol 2004; 28:1336-40.
8. Hirokawa M, Carney JA, Goellner JR, DeLellis RA, Heffess CS, Katoh R, Tsujimoto M, Kakudo K. Observer variation of encapsulated follicular lesions of the thyroid gland. Am J Surg Pathol 2002; 26:1508-14.
9. Renshaw AA, Gould EW. Why there is tendency to "overdiagnose" the follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2002; 117:19-21.
10. Chan JK. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2002; 117:16-8.
11. Baloch ZW, Livolsi VA. Follicular-patterned lesions of the thyroid: the bane of the pathologist. Am J Clin Pathol 2002; 117:143-50.
12. Elsheikh TM, Asa SL, Chan JK, DeLellis RA, Heffess CS, LiVolsi VA, Wenig BM. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. Am J Clin Pathol 2008; 130:736-44.
13. Logani S, Gupta PK, LiVolsi VA, Mandel S, Baloch ZW. Thyroid nodules with FNA cytology suspicious for follicular variant of papillary thyroid carcinoma: follow-up and management. Diagn Cytopathol 2000; 23:380-5.
14. Zacks JF, de las Morenas A, Beazley RM, O'Brien MJ. Fine-needle aspiration cytology diagnosis of colloid nodule versus follicular variant of papillary carcinoma of the thyroid. Diagn Cytopathol 1998; 18:87-90.
15. Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, Vielh P, DeMay RM, Sidawy MK, Frable WJ. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008; 36:425-37.
16. Baloch ZW, LiVolsi VA. Our approach to follicular-patterned lesions of the thyroid. J Clin Pathol 2007; 60:244-50.
17. Cancer Genome Atlas Research N. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014; 159:676-90.
18. Asa SL, Giordano TJ, LiVolsi VA. Implications of the TCGA genomic characterization of papillary thyroid carcinoma for thyroid pathology: does follicular variant papillary thyroid carcinoma exist? Thyroid 2015; 25:1-2.
19. Wreesmann VB, Ghossein RA, Hezel M, Banerjee D, Shaha AR, Tuttle RM, Shah JP, Rao PH, Singh B. Follicular variant of papillary thyroid carcinoma: genome-wide appraisal of a controversial entity. Genes Chromosomes Cancer 2004; 40:355-64.
20. Xu B, Ghossein R. Encapsulated thyroid carcinoma of follicular cell origin. Endocr Pathol 2015; 26:191-9.
21. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. Thyroid 2013; 23:273-9.
22. Baloch ZW, Shafique K, Flannagan M, Livolsi VA. Encapsulated classic and follicular variants of papillary thyroid carcinoma: comparative clinicopathologic study. Endocr Pract 2010; 16:952-9.
23. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26:1-133.
24. Hodak S, Tuttle RM, Maytal G, Nikiforov YE, Randolph G. Changing the cancer diagnosis: the case of follicular variant of papillary thyroid cancer-primum non nocere and NIFTP. Thyroid 2016; 26:869-71.
25. Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, Hwang S, Berry DA, Kinzler KW, Black WC, Bissell M, Parnes H, Srivastava S. Addressing overdiagnosis and overtreatment in cancer: a prescription for change. The Lancet Oncology 2014; 15:e234-42.
26. Fukunaga M, Shinozaki N, Endo Y, Ushigome S. Atypical adenoma of the thyroid. A clinicopathologic and flow cytometric DNA study in comparison with other follicular neoplasms. Acta Pathologica Japonica 1992; 42:632-8.
27. de la Salmoniere P, Lange F, Hoang C, Louvel A, de Roquancourt A, Vilde F, Hejblum G, Chevret S, Chastang C, Tzen CY. Is atypical follicular adenoma of the thyroid a preinvasive malignancy? Hum Pathol 2003; 34:1092-100.
28. Kakudo K, Wakasa T, Kakudo M, Liu Z. Borderline and precursor lesions of thyroid neoplasms: a missing link. J Basic Clin Med 2015; 4:2-7.
29. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, Barletta JA, Wenig BM, Al Ghuzlan A, Kakudo K, Giordano TJ, Alves VA, Khanafshar E, Asa SL, El-Naggar AK, Gooding WE, Hodak SP, Lloyd RV, Maytal G, Mete O, Nikiforova MN, Nose V, Papotti M, Poller DN, Sadow PM, Tischler AS, Tuttle RM, Wall KB, LiVolsi VA, Randolph GW, Ghossein RA. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016; 2(8):1023-9.

30. Baloch ZW, Wu H, LiVolsi VA. Post-fine-needle aspiration spindle cell nodules of the thyroid (PSCNT). Am J Clin Pathol 1999; 111:70-4.
31. LiVolsi VA, Merino MJ. Worrisome histologic alterations following fine-needle aspiration of the thyroid (WHAFFT). Pathol Annu 1994; 29:99-120.
32. Kakarmath S, Heller HT, Alexander CA, Cibas ES, Krane JF, Barletta JA, Lindeman NI, Frates MC, Benson CB, Gawande AA, Cho NL, Nehs M, Moore FD, Marqusee E, Kim MI, Larsen PR, Kwong N, Angell TE, Alexander EK. Clinical, sonographic, and pathological characteristics of RAS-positive versus BRAF-positive thyroid carcinoma. J Clin Endocrinol Metab 2016; 101:4938-44.
33. Barroeta JE, Baloch ZW, Lal P, Pasha TL, Zhang PJ, LiVolsi VA. Diagnostic value of differential expression of CK19, Galectin-3, HBME-1, ERK, RET, and p16 in benign and malignant follicular-derived lesions of the thyroid: an immunohistochemical tissue microarray analysis. Endocr Pathol 2006; 17:225-34.
34. Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. Mod Pathol 2016; 29:698-707.
35. Baloch ZW, LiVolsi VA. Encapsulated follicular variant of papillary thyroid carcinoma with bone metastases. Mod Pathol 2000; 13:861-5.
36. Valderrabano P, Khazai L, Leon ME, Torres N, Jackson R, McCaffrey T, Otto K, Centeno BA, McIver B. Non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) have very low but real malignant potential (abstract). American Thyroid Association Annual Meeting 2016; 26:P-1-A-129.
37. Faquin WC, Wong LQ, Afrogheh AH, Ali SZ, Bishop JA, Bongiovanni M, Pusztaszeri MP, VandenBussche CJ, Gourmaud J, Vaickus LJ, Baloch ZW. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in The Bethesda System for Reporting Thyroid Cytopathology. Cancer Cytopathol 2016; 124:181-7.
38. Maletta F, Massa F, Torregrossa L, Duregon E, Casadei GP, Basolo F, Tallini G, Volante M, Nikiforov YE, Papotti M. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. Hum Pathol 2016; 54:134-42.
39. Bizzarro T, Martini M, Capodimonti S, Straccia P, Lombardi CP, Pontecorvi A, Larocca LM, Rossi ED. Young investigator challenge: the morphologic analysis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features on liquid-based cytology: some insights into their identification. Cancer 2016; 124:699-710.
40. Canberk S, Gunes P, Onenerk M, Erkan M, Kilinc E, Kocak Gursan N, Kilicoglu GZ. New concept of the encapsulated follicular variant of papillary thyroid carcinoma and its impact on the Bethesda System for Reporting Thyroid Cytopathology: a single institute experience. Acta Cytol 2016; 60:198-204.
41. Strickland KC, Howitt BE, Marqusee E, Alexander EK, Cibas ES, Krane JF, Barletta JA. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. Thyroid 2015; 25:987-92.
42. Epstein JI. International Society of Urological Pathology (ISUP) Grading of Prostate Cancer: author's reply. Am J Surg Pathol 2016; 40:862-4.
43. Lagios MD. Duct carcinoma in situ: biological implications for clinical practice. Semin Oncol 1996; 23:6-11.
44. Tang P, Teichberg S, Roberts B, Hajdu SI. Ultrastructure of the periductal area of comedo carcinoma in situ of the breast. Ann Clin Lab Sci 2001; 31:284-90.
45. Likhterov I, Osorio M, Moubayed SP, Hernandez-Prera JC, Rhodes R, Urken ML. The ethical implications of the reclassification of noninvasive follicular variant papillary thyroid carcinoma. Thyroid 2016; 26:1167-72.