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Evolution of the Histologic Classification of Thyroid Neoplasms and its Impact on Clinical Management

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Abstract

The vast majority of low grade follicular cell derived thyroid carcinomas follows an indolent clinical course and is associated with very low mortality. Risk stratification using multiple clinical and pathologic characteristics has become the standard of care to guide appropriate management and avoid overtreatment. Over the past few decades, the field of thyroid pathology has witnessed several major changes that significantly impacted upon patients' care. These are: 1) The reclassification of non-invasive encapsulated follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary-like nuclear features; 2) the diagnosis of Hurthle cell carcinoma based on the presence of capsular and vascular invasion; 3) a detailed definition of poorly differentiated thyroid carcinoma, taking into consideration mitosis and necrosis; and 4) the emphasis on a detailed pathologic analysis such as the extent of vascular invasion and extrathyroidal extension. This review describes these histological concepts and details the history, rationale, and clinical impacts of such changes. These shifts in the classification and characterization of thyroid carcinoma provided a platform supporting therapy de-escalation. In addition several lessons were learned from these changes especially from the misclassification of the non-invasive encapsulated follicular variant of papillary thyroid carcinoma. We hope that the lessons learned will help better classify tumors in the future whether arising in the thyroid or other organs.

Keywords

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); Hurthle cell carcinoma; poorly differentiated thyroid carcinoma; extensive vascular invasion; extrathyroidal extension

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Introduction

Thyroid carcinoma is the most common endocrine malignancy and the cancer with the largest annual increase in incidence in the United States [1, 2]. Over the past decades, it has become evident that the majority of low grade follicular cell derived carcinomas, in particular those that are small and organ confined, follow a highly indolent clinical course and rarely cause death. Hence, several renowned organizations, e.g. the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN), have published guidelines advocating for risk stratification and conservative management based on a number of clinical and pathologic features [3, 4]. The pathologic parameters included in the initial risk stratification are histologic type and variant, capsular invasion, the presence and extent of vascular invasion (VI) and extrathyroidal extension (ETE), the number of lymph nodes with metastatic disease, and the size of metastatic foci [3, 4]. It becomes increasingly important for pathologists to report these parameters, and for clinicians to understand the potential impact of such on patients' management. The current review intends to summarize the major changes that occurred in thyroid pathology in the past few decades with a special emphasis on those that provided the basis for de-escalation of therapy.

Reclassification of the Follicular variant of papillary thyroid carcinoma (FVPTC) as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

To understand the reclassification of this entity, one has to follow the evolution of the classification of thyroid carcinomas of follicular cell origin (Fig 1). In the 1950s and 1960s, the histopathologic diagnosis of thyroid tumors was much simpler than it is today [5]. There were thyroid carcinomas forming papillae and those making follicles, and tumors were classified into papillary, follicular and mixed papillary follicular carcinomas according to the predominant growth pattern [6]. By 1960, however, some pathologists began to realize that mixed papillary and follicular carcinomas behaved as papillary carcinomas [7]. Stuart Lindsay was the first to clearly report that cytologic nuclear alterations were the common denominator linking papillary growing tumors with a subset of follicular patterned carcinomas. In a lengthy scientific article "Carcinoma of the thyroid gland" published as a book in 1960 [8], he described the distinctive nuclear features of papillary carcinoma as follows: "nuclei were... large... characterized by delicate nuclear membranes and sparse, delicate intranuclear chromatin.....so that the nuclei characteristically appeared opaque and as though composed of ground glass...folding and indentation of nuclear membranes were frequent" (page 33). He recognized that certain tumors with a follicular growth pattern had similar nuclear features of papillary carcinoma, and "not willing to initiate an entirely new classification of thyroid carcinoma at this time" (page 42) introduced the term "follicular variant of papillary carcinoma" (FVPTC) as a distinct subtype of "follicular carcinoma" (*sic*), noting that these tumors share with conventional papillary carcinomas a propensity to give rise to lymph node metastases. Two of the 31 patients with the FVPTC reported by Lindsay died of disease [8].

The notion that some “follicular” carcinomas shared both morphologic (i.e. a characteristic set of nuclear alterations) and clinical characteristics with papillary carcinoma took time to be accepted. In 1977, Chen and Rosai, reporting a small series of six meticulously analyzed cases, critically reviewed the literature and defined the follicular variant as a tumor that “resembled papillary carcinoma in its biologic behavior and all morphologic features with the exception that papillae were not present”, thereby formalizing that it belonged to the papillary, as opposed to the follicular, carcinoma family [9]. The tumors described by Lindsay and by Chen and Rosai were obvious carcinomas. Of the six patients in the series of Chen and Rosai, two died of or with disease, 5 had nodal metastasis and all had invasive tumors with absent or partial encapsulation. The clinicopathologic analysis of large series substantiated the fact that the follicular variant was an infiltrative form of thyroid cancer with the same clinical features of conventional papillary carcinoma, in spite of the fact that within the tumor papillae were uncommon or absent altogether [10]. During the 1980s, it became universally accepted that the alterations of nuclear morphology were the most important diagnostic criterion for the classification of a carcinoma as papillary. Hence, tumors with mixed papillary and follicular growth pattern were classified as papillary when they displayed such nuclear changes, regardless of the dominance of the follicular pattern [11]. In addition in the mid 1980’s, a new subset of tumors was recognized, the encapsulated follicular variant of papillary carcinoma. If it is accepted that papillary carcinoma can be diagnosed only based on alterations of nuclear morphology, and if it is true that some papillary carcinomas can be totally encapsulated, then it is also true that an encapsulated tumor entirely composed of follicles with papillary carcinoma nuclear alterations is a carcinoma, even in the absence of invasion of the tumor capsule or of blood vessels.

The new entity created by the syllogism quoted above, became a very common diagnosis, much more so than the infiltrative FVPTC described originally. A major contributing factor to the increased diagnosis of the encapsulated FVPTC was the progressive lowering of the threshold of nuclear alterations required to diagnose a tumor as papillary carcinoma [12, 13]. The lowering of this threshold progressed at a different rate in different areas of the world (highest in the US), and was associated with considerable inter- and intra-observer variation, even among thyroid pathology experts [14–17]. Because of the lack of agreement on the minimal nuclear alteration criteria required to diagnose papillary carcinoma, many nodules previously diagnosed as follicular adenoma have in the past years been labeled as encapsulated (non-invasive) follicular variant papillary carcinoma. Since the year 2000, the diagnosis of follicular adenoma had in fact become relatively infrequent in most anatomic pathology laboratories.

Conversely, the frequency of FVPTC diagnosis increased drastically over the past few decades from less than 10% in the 80s to 17 to 25% of all PTCs in the last decade, making it the second most common variant of PTC after microcarcinoma [18–20]. This trend has been confirmed by our own experience at a tertiary cancer center. The proportion of FVPTC among all PTCs raised from 19% prior to 2000 to 27% afterwards. Such increase seems to be largely attributed to the non-invasive encapsulated FVPTC (EFVPTC) as the proportion of this diagnosis among all PTCs has been steadily progressing from 7% prior to 2000, to 17% at present. In line with our experience, published literature has shown that EFVPTCs represent half to two thirds of all FVPTCs [21]. Among EFVPTCs, the noninvasive ones

account for two thirds of all EFVPTCs, whereas the remaining one third exhibit capsular and/or vascular invasion [22, 23]. Since many series did not separate encapsulated from infiltrative follicular variant papillary carcinomas, and since they included as follicular variants cases that were classic papillary carcinomas with a predominantly follicular growth, the nodal metastatic rate for the follicular variant group of papillary carcinomas was reported as high as 22% [24, 25]. It was thus assumed for more than 30 years that the encapsulated FVPTC behaved and spread like its classic counterpart. The frequent occurrence of FVPTC and the high degree of subjectivity in the interpretation of the nuclear alterations needed for a malignant diagnosis started to be felt as a problem for the routine diagnosis of thyroid nodules. A sensible reaction was the proposal formulated in the year 2000 of the “Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)”: an encapsulated tumor composed of well-differentiated follicular cells with questionable papillary carcinoma-type nuclear changes, no blood vessel invasion, and capsular invasion that is either absent or questionable” [26]. This diagnostic term gained acceptance in several European institutions but was not used in the vast majority of North American institutions [27].

Shortly after, a few papers began to indicate that the molecular profile of the follicular variant of papillary carcinoma as a whole is different from that of classical papillary carcinoma and closer to that seen in the follicular adenoma/carcinoma (FA/FC) group of tumors [28–30]. Zhu et al. found an unusually high rate of *RAS* mutations (43%) and a very low frequency of RET/PTC rearrangements (3%) in FVPTC akin FA/FC [28]. Using comparative genomic hybridization, Wreesmann et al. demonstrated that both FVPTC (59% of cases) and FA/FC (36% of cases) were commonly characterized by aneuploidy in sharp contrast to classical PTC (4% of cases) [29]. Moreover, the pattern of chromosomal aberrations in the follicular variant of PTC closely resembled that of FA/FC. Aberrations in *PPARG* were uniquely detected in FVPTC and FA/FC. Inspired by these molecular findings, Wreesmann et al. in 2004 [29] were the first to propose that FVPTC should be reclassified. Subsequently, Liu et al. in 2006 [22] studied the behavior of the FVPTC according to its encapsulated and infiltrative forms and questioned whether the encapsulated FVPTC truly belonged to the conventional papillary carcinoma family of tumors (Figure 2). In their series from the Memorial Sloan-Kettering Cancer Center (New York, NY), infiltrative FVPTC spread to lymph nodes like classical PTC, while encapsulated FVPTC behaved like the follicular adenoma/carcinoma group of tumors. Importantly, none of 43 patients with non-invasive, encapsulated FVPTC developed recurrences, including 31 patients who underwent lobectomy alone, with a median follow-up of 11.1 years. The authors stated that “if their findings are confirmed, strong consideration should be given to reclassifying encapsulated FVPTC as an entity that is close to the follicular adenoma/follicular thyroid carcinoma class of tumors. The same criteria that were used to decide whether follicular tumors are biologically benign or malignant (i.e., capsular and vascular invasion) could be applied to the evaluation of encapsulated FVPTCs. In practical terms, a lack of capsular or vascular invasion should denote a benign clinical behavior in encapsulated FVPTC”. In the last decade, many studies have confirmed these findings and clearly shown that encapsulated and well demarcated follicular variant papillary carcinomas carry no risk of recurrence or death when invasion of the tumor capsule, vessels and adjacent non-neoplastic tissue is carefully

excluded, and the tumor completely excised [23, 31–33]. Only 2 out of 352 published cases of non-invasive EFVPTC recurred [34]. However in one case, the tumor capsule was not sampled entirely while in the other the neoplasm was incompletely resected [34]. Hence, one cannot be certain of the absence of invasion in these 2 cases. This clearly emphasizes the need for a careful and generous sampling of the capsule of the tumor.

Additional studies showed that, as currently diagnosed, the encapsulated/well demarcated FVPTC has molecular alterations similar to follicular adenoma and carcinoma, characterized by the lack of BRAF mutations, a high prevalence of *RAS* mutations, and in some instances the presence of *PPARG* rearrangement [35, 36].

In 2014, the analysis of approximately 500 papillary carcinomas by The Cancer Genome Atlas research network confirmed all previous molecular studies demonstrating that the FVPTC group of tumors, invasive and non-invasive, have a RAS-like molecular signature, unlike conventional papillary carcinoma that features a BRAF^{V600E}-like profile [37].

In 2016, a landmark study has been published by a group of 31 international experts, including 24 endocrine pathologists, which investigated 109 patients with noninvasive EFVPTCs with long term follow up of 10 to 26 years [34]. None received RAI ablation. All patients were alive without disease recurrence, indicating the extreme indolent behavior and very low risk of adverse outcome in this particular group of patients. Hence, the group proposed to rename non-invasive EFVPTC as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Such nomenclature change intentionally removes “carcinoma” from the designation. This tumor will therefore be treated by lobectomy only without the need of completion thyroidectomy and RAI therapy. This will result in a significant reduction of the psychologic impact, socioeconomic and clinical (side effects of total thyroidectomy and RAI therapy) consequences of a cancer diagnosis [38]. This reclassification has been endorsed by the upcoming World Health Organization (WHO) book on the classification of endocrine tumors facilitating its use by pathologists everywhere. It is estimated that 45,000 patients worldwide will be affected each year by this change in nomenclature.

Oncocytic Hurthle cell neoplasms

Oncocytic cells, characterized by their abundant eosinophilic granular cytoplasm and hyperchromatic nuclei, have been first described in the thyroid gland by Askanazy in 1898 [39]. In the 1950s, The American Cancer Society has recommended to classify all Hurthle cell thyroid neoplasms as malignant [40]. Subsequent studies by Thompson et al. in 1974 [41] and Gundry et al. in 1983 [42] have advocated the same approach, i.e. to consider all oncocytic neoplasms as malignant irrespective of their size, and to treat such lesions with total thyroidectomy, based on a disease specific mortality of 12% in non-invasive (so called benign) and 31% in invasive (so called malignant) oncocytic tumors. Several years after, evidence has emerged that the presence of invasion, can reliably predict the behaviors and outcome of oncocytic lesions [43]. Nowadays, it becomes widely accepted that oncocytic neoplasms should be classified into Hurthle cell adenoma (i.e. benign neoplasm) and carcinoma based on the absence or presence of invasion (capsular or vascular; Figure 3).

Oncocytic adenoma, which lacks capsular or vascular invasion, or oncocytic tumor of unknown malignant behavior, which exhibits solid growth pattern and/or incomplete capsular invasion but no vascular invasion, follow a benign clinical course, with no or negligible risk of relapse or disease-specific mortality [43, 44]. Hurthle cell carcinomas are further subtyped into minimally invasive and widely invasive tumors. Minimally invasive carcinomas are usually indolent while widely invasive carcinomas are much more aggressive with a long term mortality rate around 50% [45]. Widely invasive carcinomas show obvious gross invasion including almost always invasion of multiple vessels. The definition of minimally invasive carcinomas is more controversial. While some authorities use this terminology for encapsulated HCC with microscopic invasion independently of the type (capsular or vascular) or the number of invasive foci [43, 46], others will restrict the term to those with capsular invasion only. The rationale of the latter definition is not to label HCC with vascular invasion as minimally invasive since some HCC with microscopic foci of vascular invasion can develop distant metastasis (Figure 3). Recently, studies have shown that it is the extent rather than the mere presence of vascular invasion that denotes an aggressive behavior in encapsulated low grade thyroid carcinomas of follicular cell origin including Hurthle cell carcinoma (see next paragraph) [47, 48]. Since some therapeutic guidelines, such as the ATA and NCCN [3, 4], will place an encapsulated low grade carcinoma as low risk if focal vascular invasion is present, it is imperative to report the extent of vascular invasion in HCC. Interestingly, we found that HCC with extensive vascular invasion have a different gene expression profile than those with focal or no vascular invasion [49].

Poorly differentiated thyroid carcinoma (PDTC)

In 1984, poorly differentiated thyroid carcinoma was first described by Carcangiu et al. [50] as a carcinoma with insular growth pattern and a prognosis in between the indolent well differentiated thyroid carcinoma and the extremely aggressive and often fatal anaplastic carcinomas. It was not until 2007 that a uniform set of diagnostic criteria for PDTC, namely the Turin proposal, had been put forward by a group of international thyroid experts. These are: 1) insular/solid/trabecular growth pattern; 2) the absence of nuclear features of papillary thyroid carcinoma; and 3) one or more of the following three features: convoluted nuclei, mitotic index of 3 or more per 10 high power fields, and tumor necrosis [51]. About the same time, an alternative set of criteria for PDTC, the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, was proposed based solely on a mitotic index of $\geq 5/10$ HPFs and/or tumor necrosis regardless of tumor growth patterns and nuclear features [52]. Both approaches were able to identify tumors with an intermediate prognosis with a reported mortality rate of 38 – 57% [2, 51–53]. Additionally, PDTC diagnosed using MSKCC criteria has been shown to be the main cause of disease specific death in non-anaplastic thyroid carcinoma [54] and the major contributor of radioactive iodine (RAI) refractory disease [55]. The delineation of this new entity at the histological level and its propensity to give rise to RAI refractory FDG-PET positive disease has enabled clinicians to follow this tumor by more sensitive imaging modalities. Indeed, the ATA recommends the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) to initially stage patients with PDTC [3]. Also clinicians should be aware that they cannot always rely on serum

thyroglobulin levels to assess tumor burden in PDTC since the latter may not produce sufficient amount of this protein. In view of its intermediate prognosis, patients with PDTC have to be counseled differently than those with garden variety PTC.

In 2016, Landa et al. [56] published the genomic profile of PDTC and anaplastic thyroid carcinoma using MSKCC PDTC criteria and ultra-deep targeted exome next generation sequencing platform in a large cohort of 84 PDTC and 33 anaplastic thyroid carcinoma. Their findings, together with the genomic alterations of PTC reported by the Cancer Genomic Atlas (TCGA) network [57], have revealed a stepwise molecular progression of thyroid carcinoma from well-differentiated PTC, to PTDC, to anaplastic thyroid carcinoma (Figure 6) [58]. Similar to the well-differentiated PTC, *BRAF*^{V600E} and *RAS* mutations remain the mutually exclusive main driver mutations in PDTC, affecting 33% and 28% of cases respectively [56]. The *BRAF/RAS* signatures are also closely correlated with the histologic diagnostic criteria of PDTC: PDTCs fulfilling both Turin proposal and MSKCC criteria harbor a high frequency (42%) of *RAS* mutation, whereas 78% of PDTCs diagnosed solely by MSKCC criteria are associated with *BRAF*^{V600E} mutation (Figure 6) [56]. In addition to *BRAF* or *RAS*, PDTC contains additional molecular alterations, including high mutation burden, increased chromosomal complexity, frequent *TERT* promoter mutation (40%); *EIF1AX* mutation (11%); mutations in tumor suppressor genes, e.g. *TP53* (8%) and *ATM* (7%); alterations in PI3K/AKT/mTOR pathway (11%), SWI/SNF chromatin remodeling complex (6%), histone methyltransferases (7%), and mismatch repair pathway (2%), as well as widespread somatic copy number alteration (e.g. gain of chromosome 1q and loss of chromosomes 1p, 13q, 15q, and 22q) [56, 59]. Lastly, several molecular events may serve as adverse prognostic markers in PDTC, which include mutation burden, *EIF1AX* mutation, and chromosome 1q gain. These molecular findings may help develop therapies for patients with PDTC who not uncommonly fail conventional treatment.

From the above data, it is clear that the description of this entity at the histological and molecular level has impacted on the management of non-anaplastic thyroid carcinomas and introduced the concept of intermediate prognosis follicular cell derived thyroid carcinoma.

Extent of vascular invasion and extra-thyroid extension

In the modern era, a pathology report requires the inclusion of numerous prognostically relevant histopathologic tumor characteristics. Thyroid carcinoma is no exception to such rules. In addition to tumor type and size, other features such as the variant of papillary thyroid carcinoma, the presence and extent of vascular invasion and extrathyroidal extension, have been shown to provide additional predictive value, and are routinely included in a standardized report [60].

The extent of vascular invasion is one criterion being adopted by several renowned clinical guidelines for initial risk stratification [3, 4]. Vascular invasion was first described in thyroid malignancy by Graham [61] in 1924. Although two groups have shown that the mere existence of VI, regardless of the extent, entails a substantial risk (being 35% in one study) of distant metastasis, a larger body of literature have shown that the extent (rather than the existence) of vascular invasion is a prognostic factor in low grade thyroid carcinomas [47,

48, 62–64]. Tumors with minimal VI (defined as a few microscopic foci by NCCN, and as less than 4 foci by ATA guidelines) are associated with a low risk of recurrence (0 – 5%) with an overall similar outcome to those without VI in low grade thyroid carcinoma (Figure 4) [47, 48, 62–64]. Based on these emerging evidences, the most recent NCCN and ATA guidelines have classified an intrathyroidal follicular thyroid carcinoma with minimal VI as low risk lesion, which does not command a completion thyroidectomy and RAI ablation therapy. On the other hand, the presence of extensive vascular invasion (≥ 4 foci) in a differentiated thyroid carcinoma will place the patient into the high risk group, which mandates total thyroidectomy and post-operative RAI therapy [3, 4]. Hence, it is important for clinicians to take into consideration the very extent of VI when making clinical decisions. While the prognostic value of VI is universally accepted in follicular and Hurthle cell carcinoma, it is still a matter of debate whether VI is an independent predictor of poor outcome in PTC [65].

Extrathyroidal extension (ETE), defined as tumor extension beyond the thyroid capsule into the adjacent tissues, is a common pathologic finding, detected in 23.5% of all papillary thyroid carcinomas [66]. ETE has long been considered as an adverse prognostic factor and is associated with an increased risk of recurrence and mortality [10, 66–68]. ETE can be further divided into two categories: minimal ETE, which is invasion into the immediate perithyroidal soft tissue or sternothyroid muscle, detected typically at microscopic level only; whereas extensive (or gross) ETE is usually established clinically during the operation and is defined as direct extension of the carcinoma into subcutaneous tissue, adjacent viscera (e.g. larynx, trachea, and esophagus), or recurrent laryngeal nerve. Based on the current American Joint Committee on Cancer (AJCC) staging system, minimal ETE is staged as T3 regardless of tumor size, while gross ETE is staged as T4a (moderately advanced disease) [69]. Under the 2015 ATA guideline, microscopic ETE is considered as intermediate risk, while gross ETE as high risk [3]. The very definition of microscopic ETE is problematic and subjective as universal pathologic criteria are lacking, and the thyroid is devoid of a well-defined capsule and often intermingled with adipose tissue or even skeletal muscle at its periphery. Not surprisingly, the interobserver agreement for minimal ETE is poor with a kappa value of 0.14 among expert endocrine pathologists [70]. From a practical point of view, this is however not a problem since recent studies have shown that minimal ETE alone does not significantly impact recurrence free survival [71, 72]. Rather, it is gross ETE that is a strong predictor for recurrence and disease specific death (Figure 5) [73, 74]. The fact that microscopic ETE does not affect survival raises concerns of whether microscopic ETE alone is sufficient to upstage a patient as T3. When deciding whether ETE should trigger additional therapy (completion thyroidectomy, RAI therapy), the pathologists and the clinician should realize that it is gross rather than microscopic ETE that worsen outcome. A knee jerk response to a pathologic report mentioning ETE without evidence of gross invasion of extra-thyroid tissue may subject the patient to unnecessary treatment especially in PTC cases [75].

Papillary thyroid microcarcinoma: an entity requiring consideration for reclassification

The reclassification of the non-invasive EFVPTC represents a paradigm shift that can be used to rename thyroid or non-thyroid neoplasms currently classified as malignant but with an extremely indolent behavior. As it was recently shown [76], subcentimeter papillary thyroid microcarcinomas are extremely indolent but often overtreated as well. Some have suggested in 2003 renaming the incidental papillary thyroid microcarcinomas as papillary microtumor [77]. This new nomenclature was however never adopted since, in contrast to NIFTP, some papillary microcarcinomas give rise to lymph node and distant metastasis [78]. If a molecular marker can help separate the rare “bad actors” from the vast majority of extremely indolent papillary microcarcinomas, then relabeling the indolent tumors will be feasible, and would greatly impact upon treatment deescalation [79].

Conclusions

The field of thyroid pathology has evolved dramatically over the past several decades. Several major changes occurred, including reclassifying non-invasive encapsulated follicular variant of papillary thyroid carcinoma as NIFTP, the introduction of the concept of poorly differentiated thyroid carcinoma, the invasion requirement to diagnose Hurthle cell carcinoma, and incorporation of numerous detailed pathologic characteristics (e.g. the presence and extent of VI and ETE) into the pathology report. These shifts in the classification and characterization of thyroid carcinoma have allowed for the de-escalation of therapy in a large number of patients with differentiated thyroid carcinoma. Importantly, several lessons were learned from these changes especially from the misclassification of the non-invasive encapsulated follicular variant of papillary thyroid carcinoma. Essentially, the analysis of the molecular profile of this tumor was essential in prompting surgical pathologists to question the position of the encapsulated FVPTC in the general scheme of thyroid tumors. The hint from the molecular data has led to a better histopathological appraisal, adding to the concept that all features of a tumor, histologic as well as genetic, have to be taken into account for proper classification [37].

Altogether, it is crucial to carefully correlate the histopathologic features of any carcinoma with tumor spread and survival. If the outcome of non-invasive encapsulated FVPTC had been meticulously analyzed over the last 30 years, many patients throughout the world would have been spared completion thyroidectomy and radioactive iodine therapy with their side effects (recurrent nerve injury, hypoparathyroidism, salivary gland damage). Patients would also have been relieved from the psychological, social and financial burden of a cancer diagnosis. Finally, we learned that using the word cancer in any diagnosis, however indolent the tumor is, has an immense impact on patients and physicians. Indeed, despite all the recommendations emanating from medical societies and large institutions for a conservative management of indolent thyroid carcinomas, the word cancer still triggers full blown therapy in low grade minimally invasive thyroid carcinomas, papillary microcarcinoma and - and until March 2016 in noninvasive encapsulated follicular variant papillary carcinomas.

Hence, the need for a nomenclature change that reflects clinical behavior. We hope that the lessons learned will help better classify tumors in the future whether arising in the thyroid or other organs.

References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *Jama*. 2006; 295:2164–7. [PubMed: 16684987]
2. Siegel R, et al. Cancer statistics, 2014. *CA: a cancer journal for clinicians*. 2014; 64:9–29. [PubMed: 24399786]
3. Haugen BRM, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid: official journal of the American Thyroid Association*. 2016; 26:1–133. [PubMed: 26462967]
4. Tuttle, RM. National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology, thyroid cancer. City: National Comprehensive Cancer Network; 2014.
5. Tallini G, et al. The History of the Follicular Variant of Papillary Thyroid Carcinoma. *The Journal of clinical endocrinology and metabolism*. 2016; jc20162976.
6. Warren, S., Meissner, W. Tumors of the thyroid gland, Fascicle 14. Washington DC: Armed Forces Institute of Pathology; 1953.
7. Woolner LB, et al. Classification and prognosis of thyroid carcinoma. A study of 885 cases observed in a thirty year period. *Am J Surg*. 1961; 102:354–87. [PubMed: 13786653]
8. Lindsay, S. Carcinoma of the thyroid gland: a clinical and pathologic study of 293 patients at the university of California hospital. Springfield Ill: Charles C Thomas; 1960.
9. Chen KT, Rosai J. Follicular variant of thyroid papillary carcinoma: a clinicopathologic study of six cases. *Am J Surg Pathol*. 1977; 1:123–30. [PubMed: 602974]
10. Carcangiu ML, et al. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer*. 1985; 55:805–28. [PubMed: 3967175]
11. Vickery AL Jr, et al. Papillary carcinoma. *Semin Diagn Pathol*. 1985; 2:90–100. [PubMed: 3843693]
12. Renshaw AA, Gould EW. Why there is the tendency to “overdiagnose” the follicular variant of papillary thyroid carcinoma. *Am J Clin Pathol*. 2002; 117:19–21. [PubMed: 11789725]
13. Chan J. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. *American journal of clinical pathology*. 2002; 117:16–8. [PubMed: 11791591]
14. Hirokawa M, et al. Observer variation of encapsulated follicular lesions of the thyroid gland. *The American journal of surgical pathology*. 2002; 26:1508–14. [PubMed: 12409728]
15. Lloyd RV, et al. Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. *The American journal of surgical pathology*. 2004; 28:1336–40. [PubMed: 15371949]
16. Elsheikh TM, et al. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. *American journal of clinical pathology*. 2008; 130:736–44. [PubMed: 18854266]
17. Rosai J. The encapsulated follicular variant of papillary thyroid carcinoma: back to the drawing board. *Endocrine pathology*. 2010; 21:7–11. [PubMed: 20066572]
18. Jung CK, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. *The Journal of clinical endocrinology and metabolism*. 2014; 99:E276–85. [PubMed: 24248188]
19. Passler C, et al. Follicular variant of papillary thyroid carcinoma: a long-term follow-up. *Archives of surgery (Chicago, Ill: 1960)*. 2003; 138:1362–6.
20. Sebastian SO, et al. Papillary thyroid carcinoma: prognostic index for survival including the histological variety. *Archives of surgery (Chicago, Ill: 1960)*. 2000; 135:272–7.
21. Proietti A, et al. BRAF status of follicular variant of papillary thyroid carcinoma and its relationship to its clinical and cytological features. *Thyroid: official journal of the American Thyroid Association*. 2010; 20:1263–70. [PubMed: 20950194]

22. Liu J, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. *Cancer*. 2006; 107:1255–64. [PubMed: 16900519]
23. Piana S, et al. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. *The American journal of surgical pathology*. 2010; 34:868–72. [PubMed: 20463572]
24. Tielens ET, et al. Follicular variant of papillary thyroid carcinoma. A clinicopathologic study. *Cancer*. 1994; 73:424–31. [PubMed: 8293410]
25. Zidan J, et al. Pure versus follicular variant of papillary thyroid carcinoma: clinical features, prognostic factors, treatment, and survival. *Cancer*. 2003; 97:1181–5. [PubMed: 12599223]
26. Williams ED. Guest Editorial: Two Proposals Regarding the Terminology of Thyroid Tumors. *Int J Surg Pathol*. 2000; 8:181–3. [PubMed: 11493987]
27. Papotti M, et al. Galectin-3 and HBME-1 expression in well-differentiated thyroid tumors with follicular architecture of uncertain malignant potential. *Mod Pathol*. 2005; 18:541–6. [PubMed: 15529186]
28. Zhu Z, et al. Molecular profile and clinical-pathologic features of the follicular variant of papillary thyroid carcinoma. An unusually high prevalence of ras mutations. *American journal of clinical pathology*. 2003; 120:71–7. [PubMed: 12866375]
29. Wreesmann VB, et al. Follicular variant of papillary thyroid carcinoma: genome-wide appraisal of a controversial entity. *Genes Chromosomes Cancer*. 2004; 40:355–64. [PubMed: 15188460]
30. Giordano TJ, et al. Molecular classification of papillary thyroid carcinoma: distinct BRAF, RAS, and RET/PTC mutation-specific gene expression profiles discovered by DNA microarray analysis. *Oncogene*. 2005; 24:6646–56. [PubMed: 16007166]
31. Widder S, et al. A pathologic re-review of follicular thyroid neoplasms: the impact of changing the threshold for the diagnosis of the follicular variant of papillary thyroid carcinoma. *Surgery*. 2008; 144:80–5. [PubMed: 18571588]
32. Vivero M, et al. Risk stratification of follicular variant of papillary thyroid carcinoma. *Thyroid: official journal of the American Thyroid Association*. 2013; 23:273–9. [PubMed: 23025507]
33. Ganly I, et al. Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant. *Hum Pathol*. 2015; 46:657–64. [PubMed: 25721865]
34. Nikiforov YE, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. *JAMA oncology*. 2016
35. Rivera M, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct BRAF and RAS mutation patterns. *Mod Pathol*. 2010; 23:1191–200. [PubMed: 20526288]
36. Howitt BE, et al. Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma. *Thyroid: official journal of the American Thyroid Association*. 2013; 23:1256–62. [PubMed: 23477374]
37. Cancer Genome Atlas Research N. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014; 159:676–90. [PubMed: 25417114]
38. Lubitz CC, et al. Annual financial impact of well-differentiated thyroid cancer care in the United States. *Cancer*. 2014; 120:1345–52. [PubMed: 24481684]
39. Askanazy M. Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung. *Dtsch Arch Klin Med*. 1898; 61:118–86.
40. Committee ACSS. Manual of tumor nomenclature and coding. 1. New York, NY: American Cancer Society; 1951.
41. Thompson NW, et al. Hurthle cell lesions of the thyroid gland. *Surg Gynecol Obstet*. 1974; 139:555–60. [PubMed: 4479589]
42. Gundry SR, et al. Total thyroidectomy for Hurthle cell neoplasm of the thyroid. *Archives of surgery (Chicago, Ill: 1960)*. 1983; 118:529–32.
43. Carcangiu ML, et al. Follicular Hurthle cell tumors of the thyroid gland. *Cancer*. 1991; 68:1944–53. [PubMed: 1913544]

44. Stojadinovic A, et al. Hurthle cell carcinoma: a critical histopathologic appraisal. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2001; 19:2616–25. [PubMed: 11352953]
45. DeLellis, RA., et al. *Pathology and Genetics of Tumours of the Endocrine Organs*. Lyon, France: IARC Press; 2004.
46. Tallini G, et al. Oncocytic neoplasms of the thyroid gland. *Acta pathologica japonica*. 1992; 42:305–15. [PubMed: 1636432]
47. Xu B, et al. Prognostic impact of extent of vascular invasion in low-grade encapsulated follicular cell-derived thyroid carcinomas: a clinicopathologic study of 276 cases. *Human pathology*. 2015; 46:1789–98. [PubMed: 26482605]
48. Ghossein RA, et al. Prognostic factors of recurrence in encapsulated Hurthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer*. 2006; 106:1669–76. [PubMed: 16534796]
49. Ganly I, et al. Genomic dissection of Hurthle cell carcinoma reveals a unique class of thyroid malignancy. *The Journal of clinical endocrinology and metabolism*. 2013; 98:E962–72. [PubMed: 23543667]
50. Carcangiu ML, et al. Poorly differentiated (“insular”) thyroid carcinoma. A reinterpretation of Langhans’ “wuchernde Struma”. *The American journal of surgical pathology*. 1984; 8:655–68. [PubMed: 6476195]
51. Volante M, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. *The American journal of surgical pathology*. 2007; 31:1256–64. [PubMed: 17667551]
52. Hiltzik D, et al. Poorly differentiated thyroid carcinomas defined on the basis of mitosis and necrosis: a clinicopathologic study of 58 patients. *Cancer*. 2006; 106:1286–95. [PubMed: 16470605]
53. DeLellis, RA., et al. *Pathology and Genetics of Tumours of Endocrine Organs*. Lyon, France: International Agency for Research on Cancer (IARC) Press; 2004.
54. Xu B, et al. Clinicopathologic Features of Fatal Non-Anaplastic Follicular Cell-Derived Thyroid Carcinomas. *Thyroid: official journal of the American Thyroid Association*. 2016; 26:1588–97. [PubMed: 27480016]
55. Rivera M, et al. Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. *Cancer*. 2008; 113:48–56. [PubMed: 18484584]
56. Landa I, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *The Journal of clinical investigation*. 2016; 126:1052–66. [PubMed: 26878173]
57. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014; 159:676–90. [PubMed: 25417114]
58. Xu B, Ghossein R. Genomic Landscape of poorly Differentiated and Anaplastic Thyroid Carcinoma. *Endocrine pathology*. 2016; 27:205–12. [PubMed: 27372303]
59. Wreesmann VB, et al. Genome-wide appraisal of thyroid cancer progression. *Am J Pathol*. 2002; 161:1549–56. [PubMed: 12414503]
60. Seethala, RR., et al. *College of American Pathologists: Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland*. City: College of American Pathologist; 2016.
61. Graham A. Malignant epithelial tumors of the thyroid, with special reference to blood vessels. *Surg Gynecol Obstet*. 1924; 39:781–90.
62. Collini P, et al. Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hurthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. *Histopathology*. 2004; 44:35–9. [PubMed: 14717667]
63. Ito Y, et al. Prognostic factors of minimally invasive follicular thyroid carcinoma: extensive vascular invasion significantly affects patient prognosis. *Endocrine journal*. 2013; 60:637–42. [PubMed: 23327839]

64. Lang W, et al. Risk factors in follicular thyroid carcinomas. A retrospective follow-up study covering a 14-year period with emphasis on morphological findings. *The American journal of surgical pathology*. 1986; 10:246–55. [PubMed: 3706611]
65. Wreesmann VB, et al. Prognostic value of vascular invasion in well-differentiated papillary thyroid carcinoma. *Thyroid: official journal of the American Thyroid Association*. 2015; 25:503–8. [PubMed: 25748079]
66. Ortiz S, et al. Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. *Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2001; 124:261–5. [PubMed: 11240987]
67. Andersen PE, et al. Differentiated carcinoma of the thyroid with extrathyroidal extension. *American journal of surgery*. 1995; 170:467–70. [PubMed: 7485734]
68. McConahey WM, et al. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clinic proceedings*. 1986; 61:978–96. [PubMed: 3773569]
69. Edge, SB., Byrd, DR., Compton, CC., Fritz, AG., Greene, FL., Trotti, A. *AJCC Cancer Staging Manual*. Springer; 2009.
70. Su HK, et al. Inter-Observer Variation in the Pathologic Identification of Minimal Extrathyroidal Extension in Papillary Thyroid Carcinoma. *Thyroid: official journal of the American Thyroid Association*. 2016; 26:512–7. [PubMed: 26953223]
71. Ito Y, et al. Minimal extrathyroid extension does not affect the relapse-free survival of patients with papillary thyroid carcinoma measuring 4 cm or less over the age of 45 years. *Surg Today*. 2006; 36:12–8. [PubMed: 16378187]
72. Shin JH, et al. Implication of minimal extrathyroidal extension as a prognostic factor in papillary thyroid carcinoma. *International journal of surgery*. 2013; 11:944–7. [PubMed: 23820062]
73. Ito Y, et al. Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. *World journal of surgery*. 2006; 30:780–6. [PubMed: 16411013]
74. Xu B, et al. Clinico-Pathologic Features of Fatal Non-Anaplastic Follicular Cell-Derived Thyroid Carcinomas. *Thyroid: official journal of the American Thyroid Association*. 2016
75. Rivera M, et al. Molecular, morphologic, and outcome analysis of thyroid carcinomas according to degree of extrathyroid extension. *Thyroid: official journal of the American Thyroid Association*. 2010; 20:1085–93. [PubMed: 20860430]
76. Vaccarella S, et al. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. *The New England journal of medicine*. 2016; 375:614–7. [PubMed: 27532827]
77. Rosai J, et al. Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal. *International journal of surgical pathology*. 2003; 11:249–51. [PubMed: 14615819]
78. Ghossein R, et al. Prognostic factors in papillary microcarcinoma with emphasis on histologic subtyping: a clinicopathologic study of 148 cases. *Thyroid: official journal of the American Thyroid Association*. 2014; 24:245–53. [PubMed: 23745671]
79. Tallini G, et al. BRAF V600E and risk stratification of thyroid microcarcinoma: a multicenter pathological and clinical study. *Mod Pathol*. 2015; 28:1343–59. [PubMed: 26271724]

Figure 1. Timeline depicting the changes in the histologic definition and classification of well differentiated thyroid carcinoma

The references pertaining to the above time points are as follows,: Lindsay S [8], Chen and Rosai [9], Williams ED et al. [80], Zhu et al. [28], Wreesmann et al. [29], Liu J et al. [22], the Cancer Genome Atlas Research Network [57], Nikiforov Y et al. [34]. PTC, papillary thyroid carcinoma; FA: Follicular adenoma; FC, follicular carcinoma; WDT-UMP, well differentiated tumor of uncertain malignant potential”; FVPTC, follicular variant of papillary thyroid carcinoma; EFVPTC, encapsulated follicular variant of papillary thyroid carcinoma; TCGA, the cancer genome atlas research network; NIFTP, noninvasive follicular thyroid neoplasms with papillary-like nuclear features.

Figure 2. Diagram and microscopic pictures of the subtypes of follicular variant of papillary thyroid carcinoma (FVPTC)

This tumor has encapsulated (commonly *RAS* mutated) and infiltrative (most frequently *BRAF* mutated) forms. The encapsulated FVPTC (EFVPTC) can be further classified based on the invasive status. The former non-invasive EFVPTC is now reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) to emphasize the indolent nature of this lesion. (A) The tumor is composed entirely of follicular architecture and exhibits nuclear features of papillary thyroid carcinoma, e.g. nuclear membrane irregularity, nuclear enlargement, chromatin clearing, and nuclear grooves. (B) A NIFTP is an encapsulated/well-circumscribed tumor without evidence of capsular or vascular invasion. C: Infiltrative FVPTC showing tumor follicles (arrow) invading in between non-neoplastic follicles.

Figure 3.

Microscopic pictures of a 4 cm encapsulated Hurthle cell carcinoma with microscopic extensive VI (7 foci) in a 44 year old male without distant disease at presentation. The patient developed bone and lung metastasis 3 years after diagnosis: A: low power view of the tumor (T) and its capsule (C) with several intra and extracapsular vessels filled with tumor (arrows). B: Medium power view of the Hurthle cells growing in nested/trabecular pattern. C: Medium power view of a tumor thrombus (arrow) hanging in the lumen of an intracapsular vessel. D: High power view showing the tumor thrombus covered by endothelial cells (arrow). In some classification schemes, this tumor would be labeled as minimally invasive. Reprinted with permission from reference [47].

Figure 4.

Extensive vascular invasion (VI) is correlated with decreased recurrence free survival in 267 patients with encapsulated low grade follicular cell derived carcinoma (log-rank test, $p < 0.001$). In contrast patients with no or focal VI (<4 vessels) have a very good outcome. Modified from reference [47] with permission.

Figure 5.

Adverse outcome (defined as the presence of disease at last follow-up) according to degree of extra-thyroid extension (ETE) in papillary thyroid carcinoma cases with adequate follow-up. Only patients with gross ETE (15 cases) had an adverse outcome. There was no survival difference between patients without ETE (11 cases) and those with microscopic (micro) ETE (31 cases). Reprinted with permission from reference [75].

Figure 6. Stepwise molecular pathogenesis of thyroid carcinomas. Genetic profiles of papillary thyroid carcinoma (PTC), poorly differentiated thyroid carcinomas (PDTC), and anaplastic carcinoma (ATC) reveal a stepwise progression of thyroid carcinoma characterized by increased mutation burden and greater frequency of mutation in *TERT* promoter, *TP53*, *EIF1AX*, PIK3CA-AKT-mTOR pathway, SWI/SNF complex, mismatch repair genes, and histone methyltransferases (HMTs). Microscopic pictures of H&E sections from PTC (top left), ATC (top right), and PDTC (top center) with upper picture representing PDTC diagnosed by the MSKCC criteria only and lower picture showing PDTC fulfilling both MSKCC and Turin proposal. Below are the rates of genetic alterations in each histotype. Reprinted with permission from reference [58].