When to use term 'follicular neoplasm of undetermined malignant potential'? A review of literature.

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1. Introduction

Follicular thyroid carcinoma is defined as a malignant epithelial tumor showing follicular cell differentiation and lacking the diagnostic nuclear features of papillary thyroid carcinoma [1]. The main problem involved in interpretation of follicular growth pattern in thyroid is the distinction between follicular nodules and follicular adenoma, between follicular adenoma and minimally invasive follicular carcinoma, and between follicular adenoma/carcinoma and the follicular variant of papillary carcinoma. Immunohistochemistry and molecular pathology for genetic profiling have been utilized in an attempt to resolve some of these issues but have not yet succeeded in attaining a level of reliability or practicality that could be translated into the routine practice of surgical pathology [2]. Follicular cell differentiation that does not usually raise any major difficulty, the two crucial issues of both definitions reside in the need to demonstrate malignancy and to exclude the presence of nuclear features typical of papillary carcinoma thyroid. For all practical purposes, the distinction between nodular hyperplasia and follicular adenoma is more of academic interest than of practical value, since both are, by definition, benign conditions. However most pathologist would restrict the diagnosis of follicular adenoma to lesions that are well encapsulated and usually solitary, and in which the uninvolved thyroid parenchyma does not display any features of nodular hyperplasia. In case of follicular carcinoma, the criteria of capsular invasion are the more difficult to apply and varies widely among practicing pathologists [3]. Some studies have indicated that capsular invasion in the absence of vascular invasion does not appear to be significantly affect the outcome of these tumors [4]. However, differentiating the grey area between follicular adenoma and minimally invasive follicular carcinoma has immediate practical consequences for the patient.
The prognosis of follicular carcinoma depends on several factors: age of the patients, size and staging of the tumors, completeness of surgery and responsiveness to radioactive iodine. It also depends on the degree of invasiveness of tumors: minimally invasive carcinomas carry a much better prognosis than do widely invasive carcinomas. The prognostic importance of angioinvasion has been recently acknowledged. The prognostic meaning of tissue cell and cell differentiation remains controversial, although it is generally accepted follicular carcinomas composed of oncocyctic cells and follicular carcinomas with a solid, trabecular or insular growth pattern respond less well to radioactive iodine and may carry a worse outcome [5]. An over diagnosis of this condition may lead to excessive treatment, including total thyroidectomy followed by radioactive iodide therapy. The most controversial lesions in the follicular variant of papillary carcinoma group are those that are encapsulated, show no invasion, and/or have multilocal or imperfect nuclear features. There still exists poor diagnostic agreement even among so-called 'expert thyroid pathologists.' It has been suggested that these be diagnosed as 'adenoma,' 'atypical adenomas,' or 'tumors of indeterminant malignant potential.' In this review we make an effort to highlight the need to use term 'follicular tumors of indeterminate malignant potential' and long term followup.

2. Macroscopy, Microscopy and Invasiveness

Minimally invasive follicular carcinomas are macroscopically indistinguishable from follicular adenoma, except for capsular characteristics; the capsule tends to be thicker and more irregular in follicular carcinoma than follicular adenoma.

Widely invasive follicular carcinoma may occur as partially encapsulated tumors with extensive penetration of the capsule or as multinodular, bulking tumors without a capsule, occasionally showing permeation of the thyroid veins. Follicular carcinomas usually occur as single tumors [6,7]. Multilocularity and recurrence in residual parenchyma after partial thyroidectomy are uncommon. The assumption that the development of such tumors is the end product of multiple oncogenic steps, thus justifying their usual appearance as single (unicentric) neoplasms [8]. The gross appearance of papillary thyroid cancer is quite variable. The lesion may appear anywhere within the gland. By definition, typical papillary carcinoma often average 2-3 cm, although lesions may be quite large or commonly subcentimeter in size. The lesions are firm and usually white in color with an invasive appearance. Lesional calcification is a common feature. Owing to the extensive sclerosis, the lesion may grossly resemble a scar; especially in small lesions, which tend to be found in subcapsular location in the gland. In fact, some lesions may be rarely almost completely cystic making diagnosis difficult [9].

Histologically, follicular carcinoma display variable morphology ranging from small/medium-sized follicles containing colloid to trabecular or solid growth pattern. The latter tends to be more frequent in widely invasive follicular carcinoma, but they can also occur in minimally invasive follicular carcinomas. It is exceedingly rare for a follicular to be composed of macrofollicles; in case one faces a capsular and/or vascular invasive follicular tumor composed of large follicles, with or without colloid, it is mandatory to look for the nuclear characteristics of neoplastic cells because the most likely diagnosis will be a (macro) follicular variant of papillary carcinoma[5]. In other words, neither architectural nor cytological atypia are reliable criteria of malignancy. This and the need to identify unequivocal signs of invasion to make a diagnosis of follicular carcinoma, renders fine needle aspiration cytology and frozen sections useless or almost useless in these settings [10].

The classification of follicular carcinoma in two categories-minimally and widely invasive- has always created a sense of a 'pathological' gap: what about tumors that are 'simply' invasive? This gap has been filled with the creation of a third group of follicular carcinoma, angioinvasive carcinomas [5]. Most authors agree that for practical (prognostic and therapeutic) purposes, it is crucial to separate minimally invasive, not angioinvasive, follicular carcinoma which carry an excellent prognosis from angioinvasive, regardless of whether it falls in the category of widely invasive follicular carcinoma [11]. Some authors believe that it is not worthwhile trying to count the number of vessels invaded by neoplastic cells in an attempt to establish a threshold separating two groups of prognostically different angioinvasive follicular carcinoma. In daily practice, one should try to detect at least one unequivocal focus of vascular invasion and, whenever this purpose is achieved, a diagnosis of angioinvasive follicular carcinoma be made. Ideal criteria for diagnosing vascular invasion is when tumor cells invading a vessel wall associated with the thrombus adherent to intravascular tumor [12]. If one detects well preserved neoplastic tissue within a vein or whenever facing dilemma 'vascular invasion or not,' search the additional sections of the capsule and stick to the following rule.

3. Molecular Biology Follicular Neoplasm

A specific translocation t(2;3) leads to the expression of PAX8-peroxisome proliferators-activated receptor-γ (PPAR-γ) chimeric protein; initial studies by Kroll and colleagues have demonstrated that this translocation is specific to follicular carcinoma [13,14]. However, follow-up studies employing immunohistochemistry and molecular biology have shown that PPAR-γ expression can occur in some cases of follicular adenoma, follicular variant of papillary thyroid carcinoma, and even benign thyroid parenchyma [15, 16]. RAS mutations are more frequent in follicular carcinoma compared with follicular adenoma; some authors have found an association between RAS mutations and clinically aggressive follicular carcinoma [17]. LOH on chromosome 10q and 3p can be seen in follicular carcinoma, suggesting a role of tum or suppressor genes in its pathogenesis [18, 19]. Even, morphometric, and flow cytometric analysis have not helped in distinguishing these lesions. Approximately 60% of follicular carcinomas will show aneuploid cell populations. Backdahl analyzed 65 follicular thyroid tumors (26 benign tumors and 39 carcinomas). He noted that of the 20 patients with cancer who survived, 19 had diploid tumors; whereas 17 of 19 patients who died of carcinoma had tumors with aneuploid DNA patterns [20,21].

Unfortunately literatures suggest that the most prominent molecular features of follicular carcinoma are also frequently observed in follicular adenoma and are therefore almost useless.
for diagnostic purposes. In addition, the molecular approaches for diagnosing malignancy in follicular tumors using high-throughput technologies (DNA microarrays, massive sequencing, etc.) did not provide diagnostically sound results. Taking into consideration the recently reported complex landscapes of somatic rearrangements in human breast cancer genomes and the more than 20000 or 30000 somatic mutations detected in individual human cancers, it may be anticipated that rather than searching for mutations by massive sequencing, it seems more sensible to progress in the diagnosis and prognosis of thyroid tumors by integrated histological and molecular approach [22]. The morphological frame is crucial for the topographical characterization of any tumor; this holds true particularly for follicular tumors of the thyroid as they epitomize the most important cancer properties: invasiveness in general and vascular invasiveness in particular. Besides 'topography,' the search for serum biomarkers may prove diagnostically useful in this setting. For the time being the time being the histological analysis of exhaustive samples of the tumor capsule is thus necessary to make the differential diagnosis in borderline cases, namely by the identification of vascular invasiveness [5].

4. Nuclear Features of Papillary Carcinoma

In the past few decades, the nuclear features have become the diagnostic hallmark of the tumor and growth pattern is of lesser or minimal importance. WHO definition of papillary thyroid carcinoma reflects this [1]. The nuclei of papillary cancer have been described as clear, ground glass, empty, or Orphan Annie eyes. These nuclei often overlap one another: Intranuclear inclusion of cytoplasm is often found. Another characteristic of the papillary cancer nucleus is the nuclear groove [23]. Even ultrastructural studies failed to answer curious morphology of the nucleus. Recent work from Italy has shown that immunohistochemical staining for the protein emerin shows distinctly different patterns between papillary carcinoma nuclei and those of normal thyroid or benign conditions. The staining was characteristic in both cytopathological and histological preparation [24]. Lesions which can show some of these nuclear characters include Hashimoto's disease, adenomatous hyperplasia, and diffuse hyperplasia as well as follicular adenomas (particularly hyalinizing trabecular tumor). In comparison in papillary carcinoma these nuclei are larger and more oval than normal follicular nuclei and contain hypodense chromatin [25].

An additional interesting question is: why is there an increased incidence of epithelial tumors (usually papillary carcinoma), especially microcarcinoma in Hashimoto disease, an autoimmune disease? In addition to the presence of psammoma bodies [30]. If only 1 of these 4 features is absent, the presence of all of the following subsidiary features would need to be encountered to establish the diagnosis: (1) presence of abortive papillae, (2) predominantly elongated or irregularly shaped follicles, (3) darkstaining colloid, (4) presence of rare nuclear pseudoinclusions, and (5) Multinucleated histiocytes in the lumen of the follicles. Unfortunately, in the present litigious climate, many pathologists and even some experts prefer to apply very lax criteria for making this diagnosis for fear of being sued for missing a malignancy. The risk of missing an aggressive malignancy, however appears to be overrated because, the majority of studies to date have shown that such tumors are not associated with any significant risk of recurrence or metastasis [28, 29].

The four major features cited by Chan for the diagnosis of encapsulated follicular variant of papillary carcinoma are (a) Oval rather than round nuclei; (b) crowding of nuclei, with lack of polarity in follicles; (c) clear or pale nuclear chromatin pattern throughout the entire lesions, or prominent nuclear grooves; and (d) presence of psammoma bodies [30]. If only 1 of these 4 features is absent, the presence of all of the following subsidiary features would need to be encountered to establish the diagnosis: (1) presence of abortive papillae, (2) predominantly elongated or irregularly shaped follicles, (3) darkstaining colloid, (4) presence of rare nuclear pseudoinclusions, and (5) Multinucleated histiocytes in the lumen of the follicles. Unfortunately, in the present litigious climate, many pathologists and even some experts prefer to apply very lax criteria for making this diagnosis for fear of being sued for missing a malignancy. The risk of missing an aggressive malignancy, however appears to be overrated because, the majority of studies to date have shown that such tumors are not associated with any significant risk of recurrence or metastasis [28, 29]. Immuno staining (HHME-1, CK19, galectin-3) or molecular studies for ret/PTC with micro dissected samples have not solved the controversy. The controversy will continue until some 'magic marker' or technique allows for better diagnostic definition [3].

5. Follicular Adenoma versus Follicular Variant of Papillary Carcinoma

Follicular variant of papillary carcinoma is a controversial entity and is defined as thyroid malignancy with a predominant or exclusive follicular growth pattern displaying the characteristic nuclear features of papillary thyroid carcinoma [27, 9]. The incidence of this variant is difficult to determine since in the past some of these lesions have been classified as follicular carcinomas or adenomas (or atypical adenomas). Tumor can be infiltrative or encapsulated. The cytological diagnosis of these lesions is often difficult as the characteristics of papillary carcinoma; most notably, they rarely contain nuclear grooves. Hence, the cytologist will often render a diagnosis of 'suspicious for malignancy' or 'follicular neoplasm, papillary carcinoma suspected.' The most difficult circumstance for diagnosis arises when these tumors are well circumscribed and encapsulated. Unfortunately, pathologists' perceptions of what constitute the characteristic features of papillary carcinoma can vary widely. Another significant problem is posed by encapsulated tumors in which the features of papillary thyroid carcinoma are only present focally or in multiple microscopic foci [28, 29].

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6. Follicular Variant of Medullary & Oncocytic Carcinoma: Mixed Tumors

These are rare tumors of thyroid. The presence of follicular or glandular structures in a medullary carcinoma can result from a true follicular pattern of growth or entrapment of neighboring follicles by invasive tumor. True follicular differentiation of C-cell tumors can occur. These are calcitonin-producing lesions [31]. The clues to the diagnosis on H&E stained slides are the nulei with neuroendocrine features and the granularity of the cytoplasm of the tumor cells. Trapped follicles appear at the edges of medullary tumor and stain for thyroglobulin by immunostains. Mixed follicular-medullary tumors are extremely rare. They show dual patterns of differentiation and dual hormone localization (Thyroglobulin, calcitonin) by immunostains [32].

Tumors with oncocytic (Hurthle cell) features may be benign (oncocytic variant of follicular adenoma) or malignant (oncocytic variant of papillary carcinoma and oncocytic variant of follicular carcinoma). Medullary and poorly differentiated carcinomas may also display oncocytic features. Hurthle cells are stuffed with the mitochondria with morphological, functional and genetic abnormalities [33]. The accumulation of the mitochondria may be due to a primary alteration of mitochondrial DNA or of nuclear DNA that encode mitochondrial enzymes. Regardless of the mechanism(s) involved in the process, a deficient mitochondrial function leads to an increased number of mitochondria through the stimulation of mitochondrial proliferation. It has been shown that most of the typical molecular features of conventional papillary carcinoma and follicular carcinoma are also present in their oncocytic counterpart [34]. The criteria used in the diagnosis of the oncocytic variants of papillary carcinoma and follicular carcinoma are those used in the diagnosis of conventional tumors, ie, mainly the nuclear characteristics in papillary carcinoma and signs of capsular and/or vascular invasion in follicular carcinomas. The prognosis of patients with the oncocytic variant of papillary carcinoma or follicular carcinoma is similar to that of patients with the respective conventional carcinoma provided the age of the patients and the staging of the tumors are comparable. From a clinical standpoint, the negative aspect of oncocytic carcinomas of the thyroid is their lesser ability to trap iodine, thus rendering them less responsive to radioactive iodine [35].

7. Well Differentiated Follicular “Tumors of Undetermined Malignant Potential”

Atypical follicular adenoma, term proposed by Hazard and Kenyon, includes only those follicular tumors that show pathologically disturbing features. These include spontaneous necrosis, unusual cellularity or numerous mitoses. On careful examination these do not show invasive characteristics [36]. The overwhelming majority of the atypical adenomas behave clinically in a benign fashion. There are two separate problems in the diagnosis of encapsulated tumors with follicular architecture: to decide whether minor nuclear changes of the papillary carcinoma type justify a diagnosis of follicular variant of papillary carcinoma and to decide whether a minor degree of capsular penetration justifies a diagnosis of malignancy [37]. For the moment and although there is no additional evidence from the molecular pathology side, we agree with Williams and the Chernobyl study group that it is more appropriate to recognize the difficulty in deciding whether the nuclei are typical than to arbitrarily place well differentiated encapsulated tumors with a follicular architecture, in which minor nuclear changes are the only indicator of a papillary carcinoma, in a definite malignant or a definite benign category. Some authors refer to these tumors simply as ‘well differentiated’ without specifying either follicular or papillary, and use the term ‘well-differentiated carcinoma, NOS’ when invasion is present [38].

A new designation ‘well-differentiated follicular tumours of undetermined malignant potential’ has been recently proposed in thyroid pathology for follicular-patterned encapsulated tumors that have been controversial. However, we believe this terminology may be extremely helpful to pathologists in the diagnosis of certain follicular-patterned lesions. This term should be used when pathologists encounter diagnostic difficulties as result of (1) questionable or minimal nuclear features of papillary thyroid carcinoma or (2) questionable or one focus of capsular invasion that is confined to tumor capsule and does not traverse the entire thickness of capsule and lacks any nuclear features of papillary thyroid carcinoma. The term ‘well-differentiated tumor of uncertain malignant potential’ should be used rarely as possible and should never be considered as substitute for adequate sampling of any follicular-patterned thyroid tumor. Studies show that these tumors are adequately treated with a conservative approach (Lobectomy or lobectomy plus isthmectomy), but one still needs firmly established management protocols [39,40].

8. Conclusions

Our review of literature suggest that, difficulties are encountered by pathologists in the diagnosis of follicular-patterned lesions of the thyroid are due to number of factors, including lack of consensus regarding diagnostic criteria, rarity of certain of the lesions, and inadequate clinicopathologic correlative studies with careful pathologic review and long term follow-up. In difficult cases it is necessary to take additional sections from capsular & pericapsular area. One should stick to ideal criteria for diagnosing vascular invasion (Tumor cells invading vessel wall associated with the thrombus adherent to intravascular tumor). Ideal criteria for diagnosing vascular invasion is when tumor cells invading a vessel wall associated with the thrombus adherent to intravascular tumor [12]. If one detects well preserved neoplastic tissue within a vein or whenever facing dilemma ‘vascular invasion or not,’ search the additional sections of the capsule and stick to the following rule. When in doubt one should categorize these tumors as follicular neoplasm of undetermined malignant potential. There is overall necessity for long term follow-up with well-planned controlled clinical outcome studies for these thyroid carcinomas of follicular origin.

Disclosure/Conflict of Interest
The author declares no conflict of interest.
9. References


