

EDITORIAL

New WHO classification of thyroid tumors: A pragmatic categorization of thyroid gland neoplasms[☆]



Nueva clasificación de la OMS de los tumores tiroideos: una categorización pragmática de las neoplasias de la glándula tiroides

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The new World Health Organization (WHO) classification of thyroid tumors¹ is the result of a pragmatic review of thyroid neoplasms in concordance with the genetic-molecular characterization of these tumors. Since the previous classification of 2004,² the molecular profile of well differentiated thyroid tumors exhibiting a follicular growth pattern has confirmed the classical classification of these tumors into papillary *versus* follicular neoplasms and benign *versus* malignant tumors.

Among the benign lesions, *follicular adenoma* (FA) remains defined as a noninvasive neoplasm presenting evidence of follicular differentiation without nuclear characteristics of papillary carcinoma. It has been considered opportune to maintain a *hyperfunctional* variant (*toxic* or *hot adenoma*), as well as other morphological

variants of FA (with *papillary hyperplasia*, with *bizarre nuclei*, *signet ring cells*, *clear cells*, *fusiform cells*, *black FA* and *lipoadenoma* [*adenolipoma*]), which merit being individualized in order to facilitate the differential diagnosis with metastatic neoplasms. The association of adenolipomas with PTEN hamartoma tumor syndrome is emphasized, particularly when manifesting in young individuals with multiple thyroid nodules.³ *Hyalinizing trabecular tumor* is another follicular neoplasm defined by its histological features. Although it shares some cytological, morphological and molecular characteristics with papillary carcinoma (PC), lymph node and hematogenous metastatic spread are exceptional.

The book includes a new chapter dedicated to “other thyroid tumors with an encapsulated follicular pattern”,

[☆] Please cite this article as: Cameselle-Teijeiro JM, Sobrinho-Simões M. Nueva clasificación de la OMS de los tumores tiroideos: una categorización pragmática de las neoplasias de la glándula tiroides. Endocrinol Diabetes Nutr. 2018;65:133–135.

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reflecting the general concern of the experts regarding the dramatic worldwide increase in the incidence of well differentiated tumors, excess diagnoses of malignancy, and unnecessary overtreatment. The pre-eminence of invasiveness (capsular and/or vascular) as a criterion for diagnosing malignancy in encapsulated well differentiated tumors is emphasized, over the nuclear characteristics of PC. The authors also recognize the difficulties that may be found in identifying invasion and/or in recognizing the nuclear features justifying a diagnosis of PC. Accordingly, in encapsulated or well circumscribed tumors exhibiting a follicular pattern and doubtful capsular or vascular invasion, independently of the presence or absence of PC nuclei (*tumors of uncertain malignant potential*), the terminology of the Chernobyl group of pathologists has been accepted.⁴ The term *follicular tumor of uncertain malignant potential* refers to encapsulated or well delimited tumors composed of well differentiated follicular cells in the absence of PC nuclei, and with questionable capsular or vascular invasion. The term *well differentiated tumor of uncertain malignant potential* refers to encapsulated or well delimited tumors composed of follicular cells with fully or partially developed PC nuclear characteristics, and with questionable capsular or vascular invasion. The cytological characteristics of *follicular tumors of uncertain malignant potential* correspond to those of the follicular neoplasms (follicular adenoma/carcinoma), while the cytological characteristics of *well differentiated tumors of uncertain malignant potential* show some PC nuclear features, and these tumors are usually classified as indeterminate (atypia of undetermined significance, follicular neoplasm or suspected PC). Although long-term follow-up data on both tumors of uncertain malignant potential are limited, the prognosis is excellent, with metastases in less than 0.2% of the cases.

Another novel category considered in the aforementioned chapter is *non-invasive follicular thyroid neoplasm with papillary-like nuclear features* (NIFTP). This is a non-invasive thyroid follicular cell tumor exhibiting a follicular growth pattern and nuclear characteristics of PC. It is a recognition of the low biological aggressivity of tumors previously classified as encapsulated (or well delimited) follicular variants of PC without capsular or vascular invasion, and of cases of *well differentiated tumors of uncertain malignant potential*. In order to ensure appropriate clinical-pathological correlation, the diagnosis of NIFTP requires compliance with the criteria described in the original publication⁵: (1) encapsulation or clear delimitation; (2) a follicular growth pattern (less than 1% papillae, the absence of psammoma bodies, and a less than 30% solid, trabecular or insular growth pattern); (3) nuclear characteristics of PC (grade 2 or 3); (4) the absence of capsular or vascular invasion; (5) no necrosis; and (6) scarce proliferative activity (fewer than 3 mitoses per ten $\times 400$ magnification fields). In the absence of data corresponding to an exhaustive examination of the tumor capsule or interface, it is advisable to use the diagnostic term "noninvasive encapsulated variant of PC" instead of NIFTP. In fine needle aspiration biopsy cytological samples, one-half of all NIFTPs are usually diagnosed as follicular neoplasm (Bethesda category IV), and the remainder as suspected malignancy (category V) or atypia of undetermined significance (category III), though rare cases may be diagnosed as PC. It is not possible to

reliably distinguish between NIFTP and PC in cytological samples. Therefore, due to the possibility of NIFTP, hemithyroidectomy is recommended instead of total thyroidectomy. Based on these criteria, patients with NIFTP can undergo lobectomy (avoiding total thyroidectomy and radioactive iodine), though incomplete tumor resection can give rise to recurrence. The probability of metastasis or other adverse effects in NIFTP is less than 1% in the first 15 years after resection. Although NIFTP shares the molecular alterations of thyroid tumors exhibiting a follicular pattern and exhibits a high prevalence of mutations of the RAS family of genes, it sometimes can be associated with fusions of the *PPARG* and *THADA* genes. It is also possible to identify *EIF1AX* and *BRAF* K601E mutations, though not the *BRAF* V600E mutation typical of conventional PC or *RET* rearrangements. The pathology report on NIFTP does not require staging, though it should include information on the size, laterality and condition of the margins of the tumor.⁶ During the current transition period it is advisable also to include a comment on NIFTP and its previous classification as noninvasive encapsulated/well delimited PC.⁶

Papillary carcinoma is defined as a malignant epithelial tumor with evidence of follicular differentiation and a series of concrete nuclear characteristics. In contrast to the previous edition,² its diagnosis also requires the presence of papillae and/or invasion.¹ Based on the clinical-pathological and molecular profile of PC, the new edition includes papillary *microcarcinoma* and the *encapsulated, follicular, diffuse sclerotizing, tall cell, columnar cell, cribriform-morular*, and *hobnail cell* variants, as well as the *fibromatosis/fasciitis stroma, solid/trabecular, oncocytic, fusiform cell, clear cell* and *Warthin type* variants. Although the WHO document¹ divides the molecular classification of the PC genome atlas⁷ into two large groups (BRAF-like and RAS-like), it also includes the main molecular characteristics of the different PC subtypes. Emphasis is also placed on the unfavorable prognosis associated with the activator mutations (C228T or C250T) in the promoter region of the *TERT* gene in well differentiated thyroid carcinomas.⁸

In relation to *papillary microcarcinoma*, which remains defined by a diameter of ≤ 1 cm, mention is made of the possibility of using the term *papillary microtumor*⁹ in reference to those cases with lesser risk. With regard to the *follicular variant* (FV) of PC, the main subtypes are described as *infiltrating FV* and *encapsulated FV with invasion*. Less frequent presentations are the *macrofollicular* and *diffuse (multinodular) FV* variants. Although there is debate as to whether the *cribriform-morular variant* is a form of PC, it represents the form of thyroid cancer found in patients with familial adenomatous polyposis.¹⁰ It is almost exclusively found in young women. While the sporadic cases generally involve solitary lesions, those associated with familial adenomatous polyposis are usually multifocal and bilateral. In this tumor, thyroglobulin immunohistochemical staining is usually weak and focal, though nuclear staining for beta-catenin is characteristic.³ The *hobnail variant* is a new and aggressive PC subtype in which over 30% of the cells exhibit hobnail features within the tumor. This tumor variant is characterized by a high proliferation index (Ki-67 $\approx 10\%$), with a frequent spread beyond the thyroid gland, recurrences, and lymph node and distant metastases. Positive

immunohistochemical staining for p53 and cyclin D1 is common, as with the *BRAFV600E*¹¹ mutation.

In turn, *follicular carcinoma* (FC) is defined as a malignant thyroid follicular cell tumor lacking the nuclear characteristics of PC. These are generally encapsulated tumors exhibiting invasive growth. In contrast to the previous classification, three main subtypes are established: (1) *minimally invasive FC* (encapsulated and with invasion only of the capsule); (2) *encapsulated angioinvasive FC*; and (3) *widely invasive FC*. These FC subtypes are directly related to the prognosis, while other FC variants such as the *clear cell*, *signet ring cell* or *glomeruloid pattern* variants are important for the microscopic differential diagnosis versus neoplasms of other organs. In the new WHO classification, oncocytic FC is considered an independent category of FC.

Due to their peculiar clinical–pathological and molecular characteristics, *Hürthle cell (oncocytic) tumors* are regarded as a separate group in the new classification of the WHO. Noninvasive oncocytic tumors are classified as *Hürthle cell (HC) adenomas*, while tumors exhibiting capsular and/or vascular invasion are classified as *HC carcinomas*. The HC carcinomas are divided into *minimally invasive*, *encapsulated angioinvasive* and *widely invasive* subtypes, following the same criteria as those applied to FC. Furthermore, a subgroup of *poorly differentiated HC carcinomas* with a poorer prognosis has been identified, which is usually resistant to radioactive iodine. The independent categorization of HC tumors will facilitate epidemiological and research studies.

Poorly differentiated carcinoma is a follicular cell tumor with limited evidence of follicular differentiation, and is morphologically intermediate between differentiated carcinomas (papillary and follicular) and anaplastic carcinoma. Although *poorly differentiated carcinoma* was considered in the classification of 2004, the inclusion of a diagnostic algorithm (Turin consensus)¹² for its definition will facilitate its distinction from the differentiated carcinomas and will reduce inter-observer variability.

The new edition has significantly expanded upon the information referring to *familial medullary and non-medullary thyroid cancer*, including both the syndromic tumor types (e.g., in DICER syndrome³) and those not associated with tumors in other locations.

Financial support

This study has been partially funded (JMC-T) by project PI15/01501-FEDER of the *Instituto de Salud Carlos III, Ministerio de Economía y Competitividad* (Spain).

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