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”.

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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 invasive-
ness (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 encap-
sulated or well circumscribed tumors exhibiting a follicular
pattern and doubtful capsular or vascular invasion, inde-
pendently of the presence or absence of PC nuclei (tumors
of uncertain malignant potential), the terminology of the
Chernobyl group of pathologists has been accepted. 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 malign-
ant 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 characteris-
tics 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 poten-
tial 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 malign-
ant potential are limited, the prognosis is excellent, with
metastases in less than 0.2% of the cases.

Another novel category considered in the aforemen-
tioned 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 malign-
ant potential. In order to ensure appropriate clinical-
 pathological correlation, the diagnosis of NIFTP requires
compliance with the criteria described in the original
publication: (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 inva-
sion; (5) no necrosis; and (6) scarce proliferative activity
(fewer than 3 mitoses per ten ×400 magnification fields). In
the absence of data corresponding to an exhaustive exami-
nation 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 diag-
nosed 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, hemithy-
rroidectomy 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 altera-
tions 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 muta-
tion typical of conventional PC or RET rearrangements.
The pathology report on NIFTP does not require staging, thou-
g it should include information on the size, laterality and
condition of the margins of the tumor. During the current
transition period it is advisable also to include a comment on
NIFTP and its previous classification as noninvasive encap-
sulated/well delimited PC.

Papillary carcinoma is defined as a malignant epithe-
lial tumor with evidence of follicular differentiation and
a series of concrete nuclear characteristics. In contrast to
the previous edition, its diagnosis also requires the
presence of papillae and/or invasion. Based on the clinical-
 pathological and molecular profile of PC, the new edition
includes papillary microcarcinoma and the encapsulated,
follicular, diffuse scleroticizing, tall cell, columnar cell,
cribiform-morular, and hobnail cell variants, as well as the
fibromatosi/fasciitis stroma, solid trabecular, onco-
cytic, fusiform cell, clear cell and Warthin type variants.
Although the WHO document divides the molecular clas-
sification of the PC genome atlas into two large groups
(BRAF-like and RAS-like), it also includes the main molec-
ular 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.

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 in reference
to those cases with lesser risk. With regard to the follic-
ular 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 cribiform-morular variant is a form of PC, it
represents the form of thyroid cancer found in patients with
familial adenomatous polyposis. It is almost exclusively
found in young women. While the sporadic cases generally
involve solitary lesions, those associated with familial ade-
nomatous 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. 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 ≈10%),
with a frequent spread beyond the thyroid gland, recur-
cences, and lymph node and distant metastases. Positive
immunohistochemical staining for p53 and cyclin D1 is common, as with the \textit{BRAFV600E} mutation.

In turn, \textit{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) \textit{minimally invasive FC} (encapsulated and with invasion only of the capsule); (2) \textit{encapsulated angioinvasive FC}; and (3) \textit{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, oncocyct FC is considered an independent category of FC.

Due to their peculiar clinical–pathological and molecular characteristics, \textit{Hürthle cell (oncocytic) tumors} are regarded as a separate group in the new classification of the WHO. Noninvasive oncocyctic tumors are classified as \textit{Hürthle cell (HC) adenomas}, while tumors exhibiting capsular and/or vascular invasion are classified as \textit{HC carcinomas}. The HC carcinomas are divided into \textit{minimally invasive, encapsulated angioinvasive} and \textit{widely invasive} subtypes, following the same criteria as those applied to FC. Furthermore, a subgroup of \textit{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.

\textit{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 \textit{poorly differentiated carcinoma} was considered in the classification of 2004, the inclusion of a diagnostic algorithm (Turin consensus)\textsuperscript{20} 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 \textit{familial medullary and non-medullary thyroid cancer}, including both the syndromic tumor types (e.g., in DICER syndrome\textsuperscript{3}) and those not associated with tumors in other locations.

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