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Review

Histopathological-molecular classifications of papillary thyroid cancers: Challenges in genetic practice settings

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Abstract

Thyroid cancer is a relatively rare disease. A literature review concerning frequencies and successive histopathological and molecular classifications of thyroid cancer was conducted to highlight new guidelines for molecular diagnostics to be implemented in practice for managing the most prevalent form of differentiated thyroid carcinomas, namely papillary thyroid cancer. Our study has shown that the frequency of thyroid cancer varies among countries, with its incidence rising faster than any other malignancy in recent decades, mainly owing to the increasing rate of detection of small cancers. Furthermore, the histopathological types of thyroid cancer have been redefined along successive WHO classifications. Indeed, to better stratify the prognosis and patient management, continuous improvements have been made to the classifications based on increasingly relevant criteria, ranging from histological structure to genetic signatures, and including cellular criteria of malignancy. In 1974, during the first edition of the WHO classifications, papillary thyroid cancer was defined as a malignant epithelial tumor containing a papillary structure. Faced with numerous issues of plethoric diagnosis and unnecessary treatments resulting from the binary distinction of thyroid proliferations into benign or malignant (in subsequent editions in 1988 and 2004), the fourth edition in 2017 added a third category, that of borderline thyroid tumors (uncertain malignant potential), with the introduction of nuclear features as major classification criteria. In the fifth edition (WHO 2022 classification), nuclear features and molecular signatures have become essential criteria, distinguishing thyroid neoplasms based on the signaling pathways involved. Thus, three groups of thyroid cancers have been separated based on mutational profiles and gene expression: 1/ the BRAFV600E-like cancer group involving BRAF V600E mutation and gene fusions involving BRAF, RET, NTRK1/3,ALK and MET; 2/ the RAS-like cancer group including NRAS, HRAS, KRAS, EIF1AX, DICER1, BRAF K601E mutations, and gene fusions involving PPARG and THADA; and 3/ the no-BRAF V600E/no-RAS-like neoplasms group involving PAX8/PPARG gene fusion and mutations in EZH1, IDH1, SOS1, SPOP, DICER1, and PTEN.

Keywords: Genetic landscape; Incidence; Molecular profiles; Papillary thyroid cancer; Cancer management; WHO classification

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1. Introduction

Thyroid cancer (TC) is a relatively rare disease whose incidence has increased faster than any other malignancy in recent decades, mainly owing to the increasing rate of detection of small cancers [1]. Differentiated thyroid carcinomas (DTC) represent the most prevalent form of TC, encompassing entities that vary histologically, molecularly and in terms of prognosis [2,3]. Risk stratification in TC is based on multiple clinical, pathological, and molecular features [4]. The standard approach to managing various types and subtypes of TC involves the use of continuously advancing anatomical, histological, and histo-molecular classifications [5]. Over the last few decades, the field of thyroid tumors has undergone significant changes, influencing its management. The high frequency of molecular abnormalities in these cancers, along with the discovery of new molecular targets and the development of drugs with a more selective action, is leading to new success in treating patients with TC [6,7].

In the following sections, a literature review was conducted, focusing on the prevalence and incidence of TC worldwide as well as the successive histopathological and molecular classifications of the most prevalent differentiated carcinomas. This includes insights from the latest fourth and fifth editions of the international classification system, aiming to highlight new guidelines for molecular diagnostics in the practical management of TC, particularly focusing on papillary thyroid cancer (PTC).

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2. Material and methods

The systematic review conducted in November 2023 aimed to comprehensively investigate TC, its frequencies and its classifications. The primary sources for this review were PubMed and Google Scholar, supplemented by other relevant literature databases and books. The search strategy employed specific terms tailored for each platform to ensure a focused and recent compilation of studies. In Google Scholar, the search query used was "(thyroid cancer) AND (classification)". For PubMed, the query included MeSH Terms such as "thyroid neoplasms" combined with various keywords related to classification. The large number of identified papers across multiple databases underscores the significance of the topic and the extensive efforts made to gather comprehensive information. The review process involved a rigorous evaluation of each study, ensuring that only relevant and high-quality research contributed to the

findings. The selection of relevant articles involved a meticulous process of analyzing titles and abstracts, followed by a comprehensive reading of the full texts to confirm their suitability for inclusion in the research.

3. Results and Discussion

Thyroid carcinomas originate from two distinct cell types within the structural and functional units of the thyroid gland known as thyroid follicles. The neuroendocrine cells responsible for producing and releasing calcitonin are called parafollicular or C cells. The primary cell type in the thyroid, known as follicular cells, plays a pivotal role in absorbing iodine and synthesizing/secreting T3 and T4 thyroid hormones. While the parafollicular C cells make up approximately 3 to 5% of thyroid-derived carcinomas, collectively known as medullary thyroid carcinomas (MTC), follicular cells constitute over 90% of carcinomas originating from the thyroid gland. MTC is a challenging disease in both diagnosis and management and it is the least common type of TC. MTC predominantly occurs sporadically, but around 25% of cases are hereditary and linked to multiple endocrine neoplasia type 2. Cancers of follicular origin are typically classified into three groups. These include well-differentiated, poorly differentiated, and anaplastic cancers. DTC includes PTC in 80 to 85% of cases and follicular thyroid cancer (FTC) in 10 to 15% of cases. Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC), both accounting for less than 2% each, represent the rarest and most aggressive forms of carcinomas derived from follicular cells [8-11].

Our review revealed variations in the frequency of TC among countries, with an increasing rate of detection of papillary microcancers. On the other hand, we revealed that the histopathological types of TC, particularly in PTC, have continuously undergone redefinitions in nearly every edition of the World Health Organization (WHO) classifications. This evolution aims to address clinical challenges associated with the dual classification of thyroid tumors as benign or malignant and to enhance the stratification of prognosis and patient management.

Prevalence and incidence of thyroid cancer

TC is a relatively rare disease, accounting for around 1% of all human cancers. Despite its rarity, it stands out as the most prevalent malignant endocrine neoplasia [12]. TC is characterized by a gender discrepancy, with a higher prevalence observed in women than in men. Affecting only 4 in 100,000 people worldwide, its rate varies across countries, with a heightened incidence noted in North America as well as in Europe [13]. Moreover, TC incidence rates reveal interesting geographical variations in North Africa. In Algeria, between 2006 and 2010, TC incidences were recorded at 1.4 per 100,000 in men and 6.2 per 100,000 in women [14]. Meanwhile, Morocco reported incidences of 1.4 per 100,000 in men and 6.7 per 100,000 in women from 2005 to 2007 [15]. In Libya, it was shown a worldwide-standardized incidence rate of 0.8 per 100,000 in men and 3.8 per 100,000 in women (Benghazi cancer registry) [16]. In Tunisia, with its comprehensive cancer registers, there are nuanced insights. In northern Tunisia (2004-2006), TC incidences were reported at 1.0 for men and 3.26 for women per 100,000 inhabitants [17]. In the province of Sousse, incidences for women were 2.8 per 100,000 between 1993 and 2006 [18]. In the southern province of Sfax (2000-2002), incidences were 0.8 for men and 2.96 for women per 100,000 inhabitants [19]. According to the cancer register for northern Tunisia, where 329 malignant thyroid tumors were observed, the sex ratio is below 1 (0.29). TC affects women slightly earlier, with mean ages of 46.7 in women and 52.3 years in men (p=0.01). In women, a high percentage (23%) of patients were aged under 35, compared with 30% in the 1999-2003 period [17].

TC is one of the cancers whose incidence has risen faster than any other malignancy in many parts of the world in recent decades [20]. In the United States, its incidence tripled from 4.5 to 14.4 per 100,000 people between 1974 and 2013. This surge is primarily attributed to the heightened detection of small TC, although a concurrent rise in the actual disease incidence remains possible. Through autopsy studies, 4 to 11% of individuals with no known thyroid disease seem to be affected by a clinically occult TC. This suggests that the more sensitive detection of subclinical disease due to the progresses in imaging systems and diagnostic protocols, have led to the identification of a growing number of cancers, with no corresponding modification in the true incidence of TC [21-25]. Indeed, in 1988-1989, 25% of newly diagnosed TC were ≤1 cm, compared with 39% in 2008-2009 [26]. This evolution in tumor size has been attributed to more early diagnosis of thyroid diseases, subsequently to the neck ultrasound increased use as well as to other more accurate imaging methods accessibility. These trends are reshaping the initial treatment and follow-up strategies for many TC patients [27].

It is noteworthy that almost all of this statistical change is attributed to an increase in the PTC incidence [28]. A study of the Olmsted County population revealed that the doubling of TC incidence between 2000 and 2012, compared with the previous decades, was entirely the consequence of the incidental detection of clinically occult PTC using imaging or pathological examination [29]. Another study predicted that in the United States in 2019, the third most prevalent cancer in women would be the papillary thyroid cancer [30]. Similarly, in South Korea, the rate of thyroid cancer diagnoses surged to a level 15 times higher in 2011 compared to 1993. This increase is linked to the widespread adoption of screening healthy individuals through neck ultrasound. However, the incidence of TC reversed with a decline for the first time in 2014, due to the reduction of screening practices [31]. In Beijing, approximately 1,099 cases of thyroid cancer were identified in 2010, leading to an incidence rate of 8.78 per 100,000 individuals. Compared with the incidence rate in 2001 (2.70 per 100,000 people), there has been a remarkable increase of 225.2% over the past nine years, equating to an annual growth rate of 14.2% [32]. In metropolitan France in 2018, an estimated 10,665 new cases of TC were reported, with women being more affected, accounting for 76% of new cases. The average age at diagnosis was around 50 [33]. On the other hand, considering that the clinical management of thyroid gland cancers primarily revolves around the

detection of nodules or cervical swellings, during neck palpation, only 5% of these nodules correspond to cancerous tumors, while the majority are likely benign (95%). This frequency increases to 7-15% of cases depending on various factors such as age, gender, medical history, exposure to radiation, family history, etc. [34,35]. In contrast, epidemiological studies indicate that based on clinical palpation, the prevalence of thyroid nodules is approximately 1% in men and 5% in women residing in regions with insufficient iodine levels [36]. Conversely, high-resolution ultrasound identifies thyroid nodules in 19 to 68% of randomly selected individuals, with a higher frequency among women and the elderly [37].

Evolution of histopathological and molecular classifications in papillary thyroid cancer

PTC is one of the slow-growing cancers that generally does not spread and can usually be cured through total thyroidectomy with or without radioactive iodine treatment (radioiodine or iratherapy) [38]. However, concerns have arisen due to the increasing population of patients with PTC, leading to worries about over-diagnosis and over-treatment of DTC. Consequently, the staging criteria used to justify therapeutic approaches have recently faced increased scrutiny [39]. To guide the treatment and prognosis of PTC, it is generally recommended to follow the guidelines of the American Thyroid Association (ATA) with risk stratification [28] or the staging manual of the American Joint Committee on Cancer (AJCC) according to TNM stage [40]. According to a recent study [41], the AJCC staging appears to be more predictive of patient survival than the ATA risk stratification system, as it classifies patients into a broader range of survival patterns [28]. Moreover, given the generally favorable prognosis of PTC at an early stage, treatment guidelines, including those from the National Cancer Institute in the United States (NIH), recommend lobectomy for tumors between 1 and 4 centimeters in size with no lymph node involvement, thus avoiding the need for lifelong hormone therapy. In very small PTC of less than one centimeter or microcarcinoma (PMTC) whose incidence is increasing, periodic ultrasound monitoring may be considered. In fact, although a common excellent prognosis, a minority of microcarcinomas were found to be clinically aggressive leading to lymph node and distant metastasis and mortality [39]. In these cases and in aggressive forms of papillary and follicular TC that persist and spread despite surgery and radioactive iodine treatment, the use of genetic markers and targeted treatments appears promising for improving prognosis [39].

Over the last decades, the field of thyroid pathology has undergone several transformations in the classification of TC [5] and a significant evolution across multiple editions of the WHO classification, from its inaugural version to the latest fifth edition in 2022. In fact, the WHO series of tumor classifications responsible of the international standards establishment serve as the essential source of clinical practice for neoplastic diseases for all organ systems (https://tumourclassification.iarc.who.int), where diagnostic criteria, histo-pathological features, and related genetic changes are defined in a disease-oriented manner. This series of WHO classifications, spanning the first edition in 1974, the second in 1988, the third in 2004, the fourth in 2017, and the latest fifth edition in 2022, reflects the relentless integration of the latest scientific and medical insights. Each edition builds upon its predecessor, refining diagnostic criteria and incorporating emerging data on the histological, genetic, and clinical features of thyroid tumors [42-47].

In the latest 5th edition of WHO classification of tumors of endocrine organs, various changes have been introduced concerning the nomenclature and histopathological diagnosis of follicular-derived thyroid neoplasms [42]. The inclusion of molecular information in recent classifications, such as specific genetic mutations associated with certain thyroid tumors, ensures a nuanced and precise characterization of subtypes, aligning therapeutic strategies with the evolving landscape of TC research. This iterative process emphasizes the commitment of the medical community to staying at the forefront of knowledge for the optimal care of patients. In fact, besides the introduction of the group of borderline thyroid tumors with uncertain malignant potential during the fourth WHO edition in 2017, the 2022 WHO classification of endocrine and neuroendocrine tumors introduced a new grading system, novel prognostic risk categories and added new thyroid tumor types and subtypes. This edition highpoint the molecular profile of well-differentiated histotypes as well as the international standards of the practical integration of both morphological and molecular characteristics of thyroid gland tumors [42].

For history, in 1974, during the first edition of the WHO classifications, papillary thyroid cancer was defined as a malignant epithelial tumor containing a papillary structure, irrespective of nuclear features. Faced with numerous issues of plethoric diagnoses and unnecessary treatments resulting from the binary distinction of thyroid proliferations into benign or malignant in subsequent second and third editions in 1988 and 2004, nuclear features were introduced as essential criteria for malignancy. In fact, PTC was defined as a malignant epithelial tumor with, in 1988 evident follicular cell differentiation showing both papillary and follicular structures, along with distinct nuclear changes and in 2004 with evidence of follicular cell differentiation and a distinct set of nuclear features. Nevertheless, consensus on precise morphological criteria for the set of typical nuclear characteristics of PTC has not been achieved among pathologists, leading to substantial inter-observer variation in the PTC diagnosis. Nuclear characteristics and molecular signatures have become essential criteria in subsequent classifications, as seen in the 2017 and 2022 editions.

The WHO 2017 classification

Besides the genetic description of follicular-derived thyroid tumors, the most significant changes included in the fourth 2017 WHO classification (in comparison to the third WHO edition of 2004) were [44-50]:

- Introduction of tumors of uncertain malignant potential (UMP) leading to a novel classification of encapsulated well-differentiated follicular thyroid tumors
- Reclassification of some thyroid tumors as borderline with the establishment of three new entities: uncertain malignant potential, non-invasive follicular thyroid neoplasm with

papillary-like nuclear features and hyalinizing trabecular tumor called respectively UMP NIFTP and HTT.
- Identification of new variants of PTC of a more aggressive biological behavior and PTC that be related to hereditary tumor syndromes.
- Sub-classification of FTC, which were divided into FTC with capsular invasion only called minimally invasive FTC, encapsulated angio-invasive FTC and widely invasive prognostic FTC categories.
- Down graduation of minimally invasive FTC of low-risk to borderline tumor based on more strict criteria for capsular and vascular invasion. This category was designed as FT-UMP for follicular tumor of uncertain malignant potential. This measure was proposed for decreasing over-treatment of low-risk FTC.
- Changes in terminology for PTC characterized by solid growth without tumor necrosis and/or increased mitosis. Belonging to PDTC, this tumor became a solid variant of PTC belonging to aggressive PTC variants.
- Changes in terminology for PDTC initially recognized as a distinct entity in the third 2004 WHO classification. PDTC was redefined using the Turin consensus criteria for its histopathological identification. Turin consensus criteria describes PDTC based on three features: the existence of solid, trabecular or insular growth pattern, the absence of PTC conventional nuclear features and the presence of at least one of the following three nuclear features: convoluted nuclei, mitotic activity superior or equal to three per ten high power fields (HPF), and tumor necrosis.
- Introduction of a new specific chapter for Hürthle cell or oncocytic cell adenoma/carcinoma tumors with precise description of their biological and clinical characteristics.
- Changes in terminology for oncocytic types of follicular adenoma and follicular carcinoma, to Hűrthle cell adenoma and carcinoma, respectively.
- Changes in terminology for the undifferentiated (anaplastic) carcinoma that was changed to anaplastic thyroid carcinoma; for the mixed medullary and follicular cell carcinoma that was changed to mixed medullary and follicular thyroid carcinoma, and for carcinoma showing thymus-like differentiation that was reclassified as intra-thyroid thymic carcinoma.

In the 2017 WHO classification, the definition of PTC underwent modification, incorporating the statement "PTC is usually invasive." Simultaneously, with the introduction of the new borderline tumor category, the diagnosis of encapsulated tumors as PTC was eliminated. Consequently, PTC was declared as a malignant epithelial tumor demonstrating features of follicular cell differentiation and a distinct set of nuclear features. Its invasiveness necessitates the presence of papillary architecture, indicators of invasion, cytological features associated with PTC or *BRAF* V600E mutation. The diagnostic criteria for PTC encompass a spectrum of histological features and growth patterns, leading to the recognition of numerous PTC variants. Among them, three aggressive variants (variant*) are of undisputable clinical reputation and are characterized by a poorer prognosis than encapsulated PTC, since patients with these tumors have an intermediate risk of recurrence. Moreover, the identification of the true biological nature of two tumors, which are the NIFTP and the WDT-UMP for well-differentiated tumors of uncertain malignant potential, is not yet accurate. Thus, the majority of encapsulated PTC without clear invasion including WDT-UMP and NIFTP have been downgraded to borderline tumors, to reduce over-diagnosis and overtreatment of low-risk PTC [44,50]. PTC variants may be listed as:
- Microcarcinoma (≤1 cm in diameter)
- Classic variant
- Follicular variant
- Encapsulated variant
- Diffuse sclerosing variant
- Cribriform-morular variant
- Tall cell variant*
- Hobnail variant*
- Columnar cell variant*
- PTC with fibromatosis/fasciitis-like stroma variant
- Solid/trabecular variant
- Oncocytic variant
- Spindle cell variant
- Clear cell variant
- Warthin-like variant

The 2017 WHO classification highlighted the prognostic significance of specific genetic markers in TC. However, the correlation between nuclear features alone and genetic alterations, including RET/PTC rearrangements, *BRAF* V600E mutation, and other *RAS* mutations, has not been consistently established [45-50]. As per the American Association of Endocrine Surgeons Guidelines (2020), the testing of *BRAF* V600E and TERT promoter mutations were not recommended for first risk stratification. However, it was shown that these mutations are linked with a high risk of recurrence in the 2015 ATA risk classification [51].

The WHO 2022 classification

In the WHO 2022 classification, several improvements have been made regarding the nomenclature of follicular-derived thyroid neoplasms as well as their histopathological diagnosis criteria. Three prognostic risk categories and three molecular groups were recognized. [42]. Thyroid neoplasms were classified into benign, low-risk and malignant tumors and into BRAFV600E-like, RAS-like and no-BRAFV600E/no-RAS-like tumors based on the molecular profile of well-differentiated histotypes. Moreover, the term "variant" used to describe a subclass of tumors has been replaced by the term "subtype. Whereas the term "variant" was exclusively reserved for describing genetic alterations [46]. The subdivision of TC into prognostic risk categories without an exact categorization, but with a list of histotypes seems to place greater emphasis on integrating both histological and genetic characteristics of thyroid tumors [42]. In this fifth edition of WHO classification, besides the particular consideration of genetic profiles, the most significant changes included:
- Particular attention to benign thyroid lesions including a comprehensive definition of the multinodular goiter with the introduction of the term of thyroid follicular nodular disease (FND). In fact, according to the occurrence of clonal genetic changes the nodules of multifocal hyperplastic/neoplastic lesions can be both hyperplastic and neoplastic.
- Insertion in the category of benign tumors of the follicular adenoma (FA) with papillary architecture but without papillary-like nuclear features and the oncocytic adenoma

(OA) (composed by >75% oncocytic cells) with substitution of the term "Hürthle cells" by the term "oncocytic cells".
- Inclusion within the class of low-risk neoplasms, the three borderline entities of the fourth WHO edition: UMP (FT-UMP and WD-UMP), NIFTP and HTT.
- Introduction of the term "high-grade DTC". The differentiated high-grade thyroid carcinoma (DHGTC) is defined as any DTC showing tumor necrosis and/or ≥ 5 mitosis per two mm^2, which is approximately equivalent to ten HPF.
- Establishment of a grading system, considering the Ki67 index, the number of mitoses and/or the presence of necrosis, to ascertain high-grade carcinomas derived from follicular cells and MTC with possible mixed follicular cell-derived and medullary carcinomas. Irrespective of TNM stage; RET mutational status and various additional clinical parameters, this histological classification system is presented as a poorer outcome independent predictor.
- Redefinition of cribriform-morular as well as invasive encapsulated follicular variants of PTC as distinctive tumors, due to unique molecular changes and clinic-pathological features, setting them apart from other PTC subtypes.
- Introduction of two new subtypes that are the thyroid tumors of uncertain histogenesis and the thyroid carcinomas of the salivary gland type.

Hence, the PTC subtypes (previously named variants) have remained without changes, excepting the expulsion of the invasive encapsulated follicular variant PTC (IEFV-PTC) from PTC group. However, there were more cytological details regarding the definition of the tall cell subtype, the solid PTC subtype, the hobnail variant PTC, and the infiltrative follicular subtype (IF-PTC) very comparable to the classical type C-PTC at the level of its infiltrative growth pattern, but showing almost fully a follicular architecture. In MPTC, the histo-morphologic features have been considered more appropriate than the tumor size.

Molecular landscape of thyroid cancer and challenges in genetic practice settings

The establishment of the molecular classifications gathering the most frequent genetic events in PTC was progressive and based on the data of the pioneer TCGA project, which was the first pan-genomic study of TC [56] as well as other similar projects and studies. In the 2022 WHO classification, the defining characteristics of PTC subtypes are no longer just based on nuclear alterations but rather on the molecular features of the tumor. In addition, to high point the potential therapeutic importance of detecting *BRAF* V600E mutations/*RET* fusions in PTC and *NTRK1/3/ALK* fusions in PTC/FTC, a well-adjusted approach was adopted. In other words, well-differentiated TC can be defined according to their genetic landscape. The C-PTC and the other PTC subtypes involving the IF-PTC display a BRAF-like phenotype. Whereas, the FTC as well as the IEFV-PTC (no more belonging to the PTC category) display a RAS-like phenotype (Table 1). However, the oncocytic thyroid carcinoma (OTC) shows no BRAF-like no RAS-like molecular profile, although belonging to well-differentiated TC [52-56].

Even though the TMB for total mutational burden is minor in TC than in most other malignancies, the increasing significance of TC genetic alterations has been highlighted by The Cancer Genome Atlas (TCGA) consortium in 2014. In fact, TCGA identified molecular alterations in 97% of TC for which gene expression profile was characterized (56). The molecular rearrangements identified in the TCGA indicate that thyroid carcinogenesis involved distinct patterns mostly affecting the *MAPK/ERK* and *PI3K/AKT/mTOR* signaling pathways. Thus, their distinctive genetic alterations lead to differential constitutive activation during the initiation of the tumorigenesis and the progression/aggravation of TC. In fact, primary-driver mutations leading to thyroid carcinogenesis are BRAF/BRAF-like mutations and RAS/RAS-like mutations, which provide differential constitutive kinase activity in TC. Furthermore, RET/PTC rearrangements, the first genetic alteration assigned to PTC, activate both *MAPK* and *PI3K* signaling pathways. In the other hand, other uncommon genetic rearrangements and mutations disturb entirely distinct pathways. Supplementary genetic alterations seem to be associated with biological aggressiveness such as alterations of *TERT*, *TP53*, *PTEN*, and others genes [57]. According to Parpounas et al., *TERT* promoter perturbations seems to be the central event of a series of aggressive tumor behaviors in TC [57].

Historically, subsequently to the detection of the oncogenic role of the *BRAF*, the V600E mutation is held to be one of the central events in the PTC tumorigenesis initiation and progression. Therefore, mutational screening of the V600E in PTC was considered as a powerful tool during the clinical and therapeutic managements of patients as a diagnosis biomarker that permits to discern benign from malignant tumors and as a sensitive prognostic indicator that permits the prediction of the tumors aggressiveness and rate of recurrence. While the TCGA analysis focused only on PTC, numerous other mutations and combinations of genetic alterations have been shown, by other subsequent studies, as important actors in other subtypes of PTC as well as other tumoral proliferations of the thyroid gland during the successive steps of tumorigenesis: initiation, growth, dedifferentiation and progression to more advanced malignancy subtypes. According to a 2017 meta-analysis, the V600E mutation of *BRAF* remains the most frequent, with a rate detection between 40 and 80% of PTC [58]. In practical management of PTC, using fine-needle aspiration specimens for the *BRAF* genetic testing during the classic PTC preoperative diagnosis have been appreciated in many studies. However, it was suggested that the diagnostic value of the implementation of this practice and the use of *BRAF* mutation as a poor prognostic biomarker is challenging in low-risk PTC subtypes such as microcarcinoma with V600E mutation leading to over unnecessary treatments. Thus, according to the 2015 ATA clinical guidelines, it was stated that the V600E is not a key factor to identify PTC of intermediate or high risks as well as to predict their recurrence rate. Accordingly, *BRAF* molecular testing is not required to select the appropriate treatment modality in PTC [53]. Moreover, it was shown later that another infrequent *BRAF* mutation, which is the K601E, is mostly found in follicular variants of PTC. This mutation was similarly detected in benign thyroid adenoma. Long-term outcomes in

BRAF K601E mutated patients have been shown to be better and disease-related deaths are rare. Then again, the K601E mutation was suggested not mandatory for the diagnostic due to its relatively low predictive value [57,59]. Briefly, our review disclosed that according to the molecular landscape of TC three groups have been separated based on their mutational profiles and genes expression [55-65]:

1) The BRAFV600E-like cancer group involving *BRAF* V600E mutation and gene fusions involving *BRAF*, *RET*, *NTRK1/3*,*ALK* and *MET*;

2) The RAS-like cancer group including *KRAS*, *NRAS*, *HRAS*, *EIF1AX*, *DICER1*, *BRAF* K601E mutations, and gene fusions involving *PPARG* and *THADA.* For the non-invasive encapsulated papillary RAS-like thyroid tumor (NEPRAS), which is a papillary-like (RAS-like) nuclear features (NS: 2-3) with a papillary pattern [46] according to Ohba et al. [52-54], it is not yet included as a distinct entity in the WHO 2022 classification.

Table 1. Nomenclature and genetic profiles of follicular cells-derived carcinomas according to 2022 WHO classification prognostic risk categories

Benign lesions
• ***FND (Thyroid follicular nodular disease)*** *: DICER1, PTEN and PTEN-like syndromes*
• ***FA*** *(Follicular adenoma)*
• ***Follicular adenoma with papillary architecture*** *: TSHR, GNAS or EZH1 mutations and alterations that activate the PKA pathway: PRKAR1A mutations, DICER1 mutations/syndrome*
• ***OA (Oncocytic follicular adenoma)***
Low-risk neoplasms
• ***FT-UMP (Follicular thyroid tumors of uncertain malignant potential)***
• ***WD-UMP (Well-differentiated tumors of uncertain malignant potential)***
• ***NIFTP (Noninvasive follicular thyroid neoplasm with papillary-like nuclear features)*** *: BRAFV600E mutation is an exclusion criterion for NIFTP and a subset of NIFTP may show THADA gene fusions or PAX8/PPARG*
These three neoplasms are mostly RAS-driven, and detection of any non-RAS-like molecular signature (e.g., BRAFV600E) or high-risk molecular alterations (e.g., TERT promoter mutations) prompts re-evaluation to exclude overt malignancy.
• ***HTT (Hyalinizing trabecular tumors)*** *: Membranous Ki67 immunoreactivity and specific PAX8/GLIS1 and PAX8/GLIS3 fusions*
Malignant neoplasms
-Well-differentiated thyroid carcinomas *usually BRAF-driven or RAS-driven*
• ***PTC (Papillary thyroid carcinoma)*** *and its subtypes with MTC or* ***PMTC*** *subtype (Papillary thyroid microcarcinoma) ;* ***C-PTC*** *subtype (Classic PTC);* ***IFFV-PTC*** *subtype (Infiltrative follicular variant PTC: BRAF driven tumor) ;* ***Tall cell PTC*** *subtype;* ***Hobnail PTC*** *subtype;* ***Columnar cell*** *subtype;* ***Solid PTC*** *subtype;* ***Diffuse sclerosing*** *subtype;* ***Warthin-like PTC*** *subtype;* ***Oncocytic PTC*** *subtype*
• ***FTC (Follicular thyroid carcinoma)*** *(minimally invasive FTC, encapsulated angioinvasive FTC and widely invasive FTC) : RAS-driven*
• ***DHGTC (High-grade follicular cell-derived carcinoma)*** *: BRAF-driven or RAS-driven lesions but mostly derived from BRAF-driven PTC + additional genetic alterations including TERT promoter and TP53 gene mutations*
• ***IEFV-PTC (Invasive encapsulated follicular variant of PTC)*** *(minimally invasive; encapsulated angioinvasive or widely invasive) RAS-driven*
• ***OCA (Oncocytic carcinoma of the thyroid)*** *(minimally invasive; encapsulated angioinvasive or widely invasive) (mitochondrial DNA mutations and increased copy number alterations)*
- Poorly, undifferentiated and others thyroid carcinomas
• ***PDTC (Poorly differentiated thyroid carcinoma)*** *: Turin criteria + BRAF-driven or RAS-driven lesions but frequent abnormal RAS signaling + additional genetic alterations including TERT promoter, TP53 and micro-RNA master regulator DICER1 mutations*
• ***ATC (Anaplastic thyroid carcinoma)*** *: Recommended routine use of BRAFV600E mutation+ specific VE1 immunohistochemistry in all patients given the potential benefit of BRAF and MEK inhibitor therapies*
• ***SCC (Squamous cell carcinoma)*** *: BRAFV600E mutations and TTF1 + PAX8 immunoexpression*
• ***Salivary gland-type carcinomas of the thyroid*** *including* ***MEC (Mucoepidermoid carcinoma)*** *(with no frequent MAML2 gene rearrangements) and* ***SC (Secretory carcinoma)*** *(with ETV6/NTRK3 fusions) (possible co-occurrence with follicular cell-derived thyroid carcinomas)*
• ***Thyroid tumors of uncertain histogenesis*** *including* ***cribriform-morular thyroid carcinoma*** *driven by the Wnt pathway, most notably APC gene mutations and* ***sclerosing mucoepidermoid carcinoma with eosinophilia***
• ***Intrathyroid thymic tumors*** *including* ***thymoma*** *and* ***thymic carcinoma families*** *and* ***intrathyroidal spindle epithelial tumor with thymus-like elements***
• ***Embryonal thyroid neoplasm***
• ***Mixed medullary and follicular cell-derived carcinoma***

3) The no-BRAF V600E/no-RAS-like neoplasms group involving *PAX8*/*PPARG* gene fusion and mutations in *EZH1*, *IDH1*, *SOS1*, *SPOP*, *DICER1*, and *PTEN*. For oncocytic follicular thyroid tumors belonging to this group, there is a distinctive molecular signature associated to two genes linked to mitochondrial biogenesis: *ESRRA* and *PPARGC1A* [66] (Table 1, Fig. 1).

Recently, other types of molecular projects were conducted to delineate the genomic changes of the thyroid tumor microenvironment. Such projects revealed the landscape of transcriptional and genomic alterations in thyroid nodules [67,68]. According to an integrative analysis of a large cohort of PTC and benign thyroid nodule (BTN) from Chinese population, a 20-gene expression signature was proposed as a potential tool in clinical practice to distinguish PTC from BTN. Based on gene expression profiles and their association with clinical and histopathological features of the thyroid lesions progression from BTN to PTC, this study suggested a novel molecular classification of TC involving four classes: BRAF, CNV-enriched, immune and stromal classes [67].

More recently, PTMETA, which is the largest multi-omics study on papillary thyroid microcarcinomas, showed an unstable cohort with numerous genomic rearrangements and described a new molecular class of PTC baptized PTMC-Inf (Inf for inflammatory) profile which had a possible sensitivity to immune checkpoint inhibitors. The transcriptomic profile of PTMC-Inf included four genes: *PDL1*, *PD1*, *CTLA4*, and *IFN-γ*. Moreover, according to this study, to predict the effect of the immuno-therapies in the PTMC-Inf profile, there are four useful specific genetic biomarkers, which include a group of driver genes: *TPTE2* (a homolog of PTEN), *IGH*, *AFP*, and *TGN* genes [68].

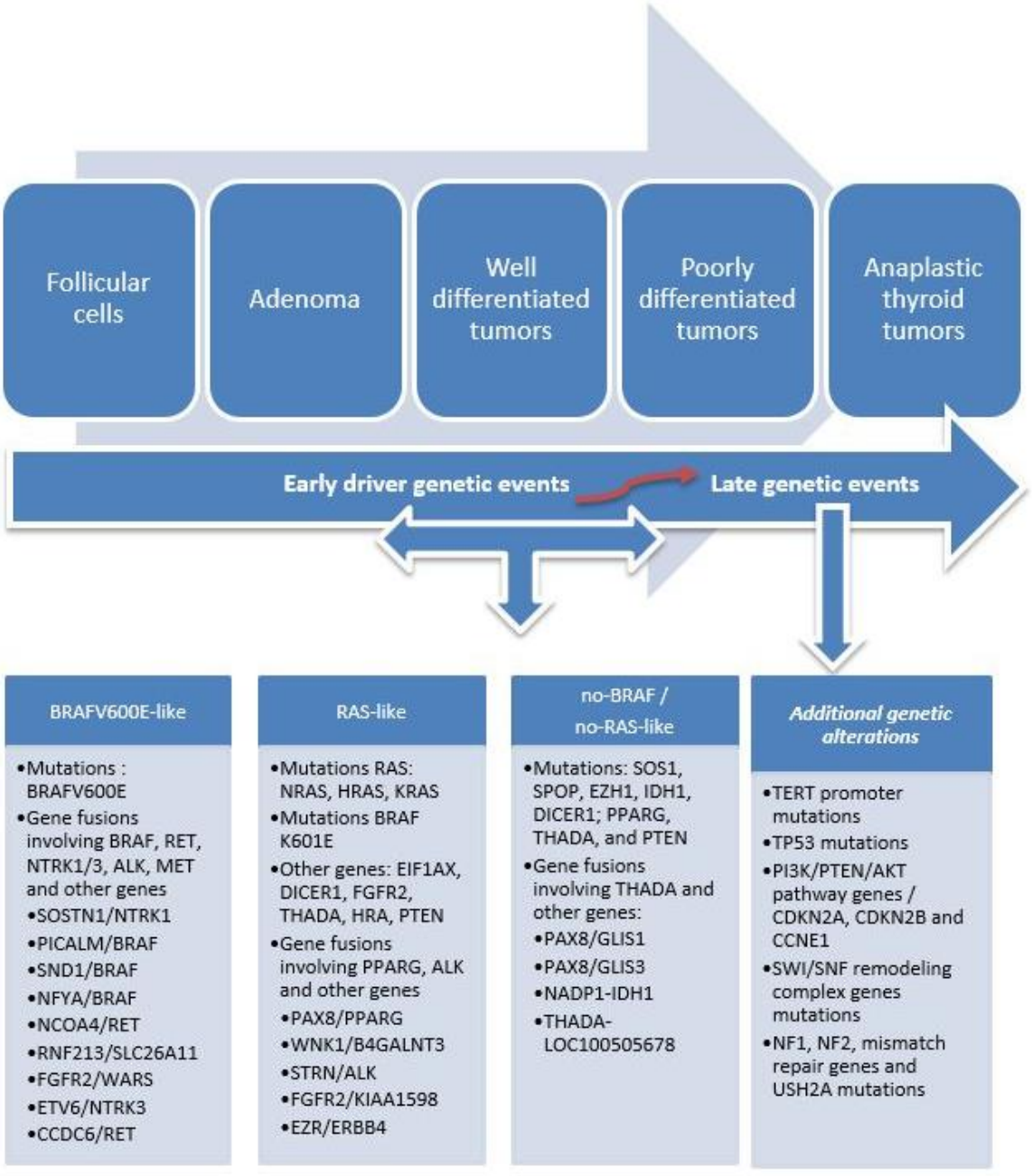

Fig.1. Genetic landscape and schematic model of follicular-derived thyroid neoplasms progression

To conclude, the evaluation of thyroid tumors is a common clinical problem, linked to the high frequency of thyroid nodules in the population. This raises concerns about the possible over-diagnosis and overtreatment of low-risk TC, given the increased detection of small and micro thyroid cancers. Consequently, the staging criteria used to justify therapeutic approaches are currently under intense scrutiny and striking the right balance in managing thyroid nodules is crucial to avoid unnecessary interventions and ensure appropriate care for those at higher risk. For precise and effective management of TC, prognostic evaluation stands out as a key strength in patient care. The WHO classifications series offers one of the most valuable frameworks that helps in diagnosing and classifying thyroid neoplasms based on their histopathological features, ensuring consistency and facilitating accurate prognostic evaluations.

The evolution of WHO classifications encompasses a continual designation of new entities and novel concepts in nomenclature and grading as well as a growing integration of genetic markers and molecular testing, contributing to advancements in the practical management of these tumors [69]. Molecular profiling is expected to play a more significant role in the coming years and integrate into clinical routines. Despite the characterization of molecular profiles of TC based on early driver mutations (changes) and those associated with aggressive progression (late event changes) as well as advances in the transcriptomic and genomic analysis of the genetic landscape of thyroid nodules, there is currently insufficient evidence regarding the clinical significance of most mutations in thyroid carcinomas to derive therapeutic implications from them.

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Declaration of Competing Interest

The authors declare that they do not have a conflict of interest.

Author contributions

Study concept and design were done by NAB, BA, IM and SA. Data were acquired by NBA, BA, IM and SA. The data were analyzed and interpreted by NBA, BA, IM and SA. Drafting of the manuscript was done by NBA and BA. All authors read and approved the final manuscript.

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