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Oncocytic Tumors in the Thyroid: A Tri-Focal Review – Integrated Cytopathological, Pathological, and Molecular Perspectives

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Abstract
Background: The thyroid gland is a treasure trove of pathology ranging from the benign to the overtly malignant. Both neoplastic and nonneoplastic thyroid lesions can exhibit oncocytic change. Here we present an overview of cytologic and histopathologic findings encountered in these oncocytic neoplasms with a focus on the molecular aspects that drive their tumorigenesis. ***Summary:*** Oncocytic change is unique to a subset of thyroid lesions ranging from nonneoplastic nodular hyperplasia to high-grade malignancy. It can also be encountered in non-follicular-derived neoplasms as well as in the adjacent parathyroid glands. At the genetic level, these lesions demonstrate a different genetic signature from classic follicular-derived lesions, often involving alterations of mitochondrial genes. ***Key Messages:*** Oncocytic change can be seen in nonneoplastic and neoplastic thyroid pathology. Rarely, oncocytic change can be seen in medullary thyroid carcinoma and certain subtypes of papillary thyroid carcinoma as well as the parathyroid gland. Oncocytic neoplasms of the thyroid harbor molecular alterations often involving mitochondrial genes, which is distinct from other thyroid neoplasia.

Introduction

The thyroid gland harbors a variety of pathology ranging from reactive metaplasia to follicular adenoma to high-grade carcinoma [1–3]. Throughout this spectrum of malignancy, one can observe oncocytic change, a phenomenon whereby the congregation of mitochondria within the cytoplasm renders an eosinophilic appearance to the cell as observed under the microscope by the pathologist [4, 5]. The thyroid gland can show oncocytes either as few scattered cells lining follicles, cellular aggregates or well-defined unencapsulated, partially or completely encapsulated nodules [6–8]. The cellular aggregates are commonly encountered in chronic lymphocytic thyroiditis as focal proliferations confined to a lobe or scattered throughout the entire gland. Similarly, oncocytic change or cellular proliferations can also be seen in euthyroid multinodular and diffuse or nodular toxic goiter [1, 5, 6, 8, 9]. Notably, oncocytic change has been described in neoplastic processes in several organ systems including the kidney, pancreas, and adrenal gland, so it is not a specific change localized to the thyroid. However, its presence should be documented as it has certain clinical implications in this organ [6, 10].

As compared to other follicular cell derived thyroid tumors, oncocytic tumors are rare. The follicular thyroid

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carcinoma comprises 5–10% of differentiated thyroid carcinomas, while oncocytic carcinoma (OCA) accounts for 3–5% [1, 6, 11]. In the 2004 edition of WHO Classification of the Endocrine Organs [12], the oncocytic tumors of the thyroid gland were classified under the umbrella term of "Oncocytic Follicular Neoplasms"; however, this was changed to "Hürthle (oncocytic) cell tumors" in the current version published in 2017 [13]. In the latest 2022 WHO classification of thyroid tumors, the nomenclature has been updated to "Oncocytic Tumors" and is defined as neoplasms comprising 75% or more oncocytic cells [2, 3].

In the early literature, some authors considered all oncocytic tumors of the thyroid gland as malignant because some of the lesions classified as benign "Hürthle cell neoplasms" behaved in a malignant fashion [14–16]. However, these findings were later disputed by reports based on strict application of diagnostic criteria to differentiate between benign and malignant oncocytic neoplasms specifically using the histopathological parameters established for follicular-patterned thyroid tumors, such as capsular and/or vascular invasion, alongside meticulous clinical follow-up [17–21]. These more detailed approaches have helped clarify the behavior of these tumors and led to a more accurate understanding of their clinical implications.

Given the increased number of mitochondria within these oncocytic cells, it is not surprising that such oncocytic lesions show greater degrees of FDG avidity than their more metabolically inert counterparts [22]. Therefore, patients with this pathology may be more likely to undergo fine needle aspiration (FNA) or biopsy to differentiate benign from malignant etiologies, particularly in incidentally identified lesions. While FNA cannot differentiate between adenoma and carcinoma, the resultant molecular studies that have become increasingly incorporated into the workflow of cytology practice can provide clues as to the nature of a tumor. In cases of malignant etiology, OCA often shows worse overall survival vis-à-vis other differentiated thyroid carcinoma [23]. Additionally, while OCA can demonstrate somatic alterations within MAPK and MTOR pathways [24], many of the oncocytic neoplasms of the thyroid are linked to alterations in mitochondrial DNA, making them genomically unique among other follicular-derived neoplasms [25–27]. Here we present a contemporary review of oncocytic lesions of the thyroid with an emphasis on the algorithmic approach to cytopathologic and histopathologic diagnosis considering molecular signatures.

Oncocytic Thyroid Lesion – Establishing the Derivation

Evaluating oncocytic lesions of the thyroid can present diagnostic challenges, particularly when limited tissue samples are available from FNA or core biopsies. To avoid common pitfalls in interpretation, certain morphological and clinical clues are essential.

Background Colloid and Cytomorphology

In FNA samples, the presence of background colloid is a significant indicator of follicular cell origin. Additionally, oncocytic follicular cells are often seen forming follicles that are partially rimmed by colloid, resembling "flame cells." These characteristics suggest a thyroid origin rather than a non-follicular tumor. When considering medullary thyroid carcinoma (MTC), the presence of amyloid deposits or spindled tumor cells can indicate the oncocytic subtype of this cancer. Recognizing these specific features can aid in differentiating it from benign oncocytic changes. In cases where the differentiation is unclear, additional tests such as measuring parathyroid hormone (PTH) levels from FNA needle rinses or performing immunohistochemistry can help clarify the diagnosis [6, 28–33].

Clinical Context

A critical aspect of cytomorphologic diagnosis is considering the overall clinical picture. A history of hypercalcemia may raise suspicion for intrathyroidal parathyroid lesions, especially if accompanied by ultrasound findings indicative of parathyroid lesion. While some oncocytic parathyroid adenomas may show minimal elevation in serum PTH levels, the clinical findings should guide further evaluation [34–36].

Benign Oncocytic Lesions

Adenomatous Oncocytic Nodules and Oncocytic Adenoma

A well-documented process in the thyroid is adenomatous nodules, colloquially referred to as "nodular goiter," a clinical term not recommended to be used in pathologic diagnosis [2, 3, 37]. It is not uncommon to encounter focal oncocytic change in most adenomatous nodules; however, some cases are exclusively comprised oncocytic cells, usually occurring in the background of chronic lymphocytic thyroiditis [38]. It is prudent to recognize that in the "recent past," such proliferation was termed as "hyperplastic"; however, molecular profiling has shown that greater than 70% of adenomatous nodules are clonal proliferations and can be associated with mutations in specific genes (*TSH*

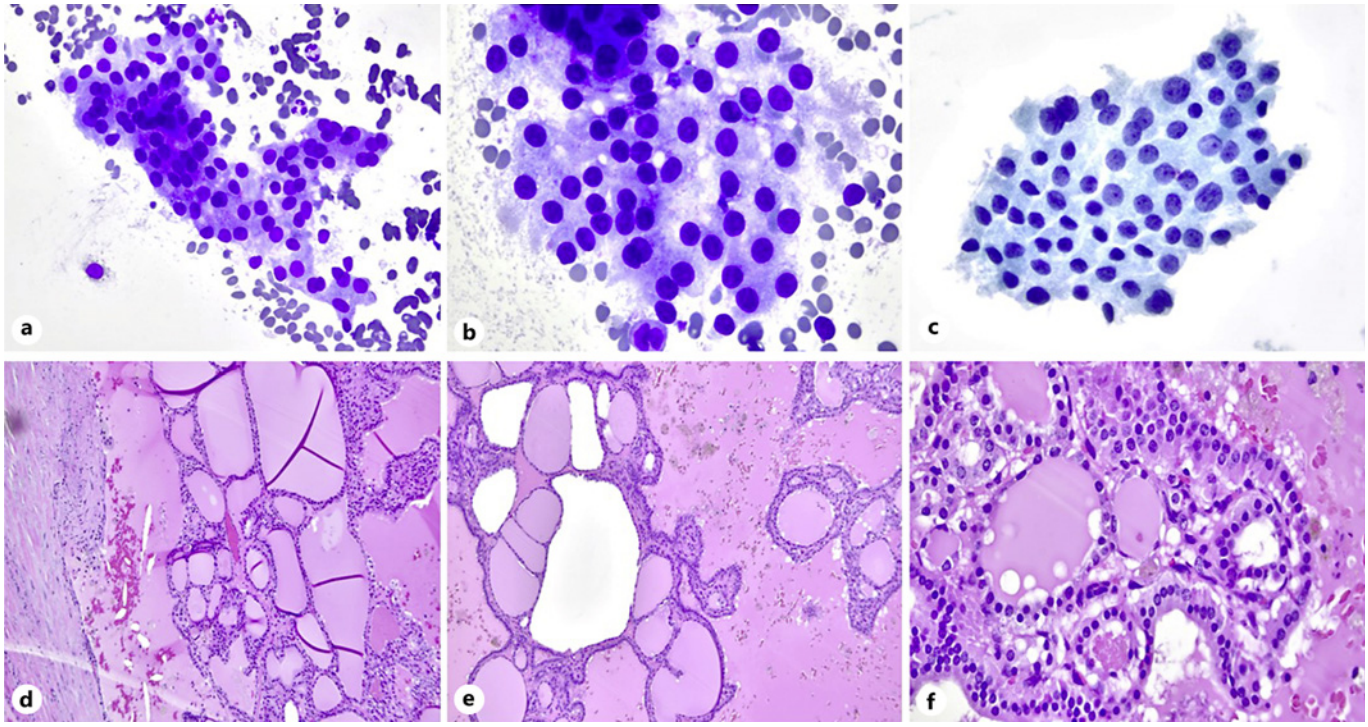

Fig. 1. Oncocytic adenomatous nodule. The FNA specimen shows a monotonous population of oncocytic cells with ample granular cytoplasm with round nuclei arranged in loosely cohesive clusters and monolayer sheet (air-dried smear preparation, Diff-Quik® stain (**a**, **b**), ThinPrep® preparation (**c**)). The surgical pathology following shows a follicular and papillary patterned encapsulated nodule with abundant watery colloid (hematoxylin and eosin stain (**d–f**)).

receptor, *GNAS*, *NAI symporter*) [3, 39–41]. On ultrasound, the adenomatous nodules are hypoechoic or hyperechoic with varying degree of extra and intramodular vascularity. The FNA specimen show a preponderance of oncocytic cells and are often classified as atypia of undetermined significance or follicular neoplasm with oncocytic features (Bethesda categories III and IV) [42, 43] (Fig. 1, 2). Therefore, the correlation with diagnostic surgical pathology is critical as it may be challenging to make this distinction on cytopathologic preparations alone given the inability to assess the entire landscape of the thyroid in FNA specimens. From a surgical pathology standpoint, these nodules are typically diffusely scattered throughout the thyroid parenchyma, most lack a well-defined capsule, differentiating them from true oncocytic adenoma (OA) [3, 6, 38]. At the molecular level, the genomic changes seen in OA (see below) are not found adenomatous nodules [44]; thus, molecular pathology can be a helpful adjunct if the distinction between hyperplasia and adenoma is inconclusive even after careful histopathologic examination. Regardless of these differences, there is essentially no clinical significance between adenomatous nodules and OA.

The OA is a specialized type of follicular adenoma with distinct molecular profile (Fig. 3). It is an encapsulated oncocytic neoplasm without evidence of capsular and/or vascular invasion, differentiating this entity from OCA [3]. Thus, distinction from carcinoma can only be made via surgical pathology with submission of the entire tumor capsule as these latter features cannot be rendered on cytologic assessment [6, 28, 45]. Something that must be considered is the propensity for OAs to infarct following FNA. Such changes following FNA, collectively referred to as *WHAFFT* (Worrisome Histologic Alteration Following Fine-Needle Aspiration), are notably frequent in oncocytic neoplasms compared to other thyroid pathologies (Fig. 4). These can include reactive atypia, inflammation, and infarction, complicating the differentiation between adenoma and carcinoma. In instances of near-total or complete infarction, it may be necessary to categorize these tumors as "oncocytic neoplasm with extensive infarction without definite evidence of invasive features," reflecting the diagnostic difficulties encountered [6, 46, 47]. Thus, careful evaluation of any necrosis and correlation with prior biopsy must be made to differentiate from bona fide tumor necrosis [3, 28, 37].

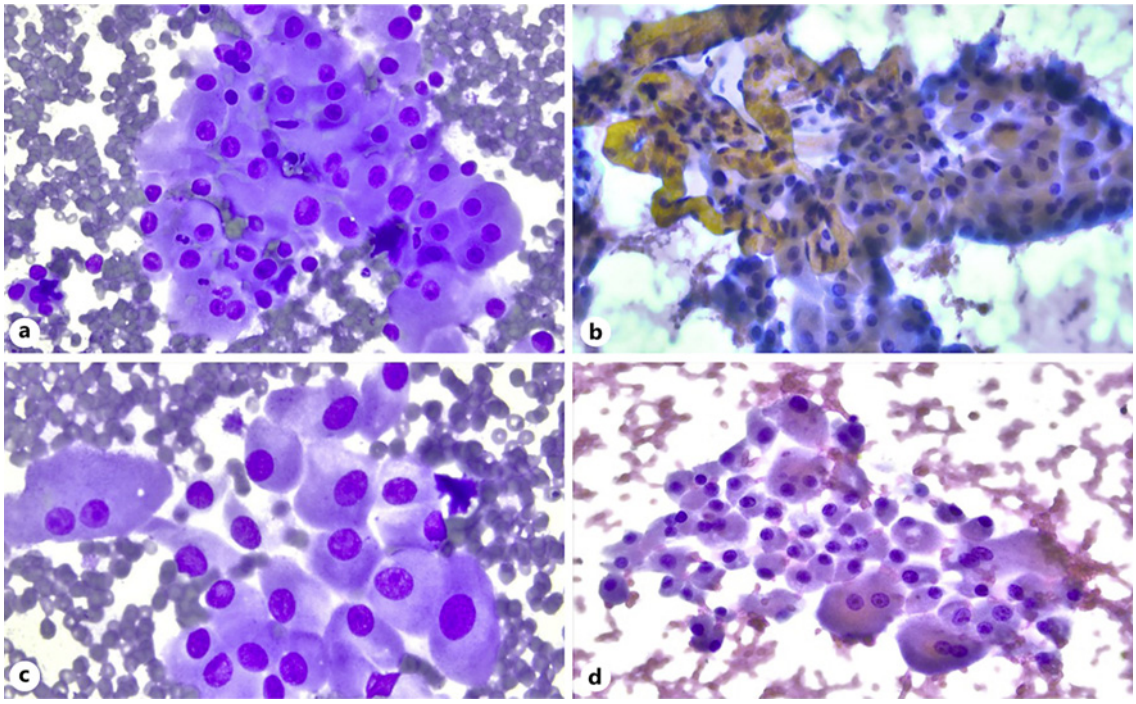

Fig. 2. FNA specimen representing an oncocytic neoplasm. The specimen shows a population of oncocytic cells shows dense cytoplasm with sharp cytoplasmic borders, round to oval shaped nuclei with prominent nucleoli (air-dried smear, Diff-Quik® stain (**a**, **b**)) The oncocytic cells are arranged in cohesive groups with transgressing vessels. The lesional cells do demonstrate random atypia in the form of variable sizes and binucleation (alcohol-fixed smear, Papanicolaou stain (**c**, **d**)).

From the molecular perspective, these tumors are genetically disparate from more traditional-appearing follicular adenomas. As mentioned previously, these neoplasms can show changes in mitochondrial genes, particularly in complex 1 subunit genes [48, 49] as well mutations in *GRIM-19*, a gene also involved in mitochondrial metabolism and cell death [26]. These tumors share some overlap with their malignant counterparts in terms of frequency of *RAS* and *EIF1AX* mutations; however, in OAs, these molecular alterations, if present, are not seen in conjunction with copy number alterations as observed in OCA [50]. In terms of prognosis, these tumors are considered benign and completely cured if totally resected, which is akin to the behavior of the classic follicular adenoma entity.

The Spectrum of Oncocytic Malignancy

OCA

Formerly known as "Hürthle cell" carcinoma, OCA of the thyroid is a specialized type of follicular carcinoma where most tumor cells (at least 75%) display an oncocytic phenotype. This neoplasm occurs in the adult population with a predominance in women [3, 23, 51, 52]. To reiterate, cytology alone cannot distinguish between OA and OCA [28].

On gross pathologic examination, oncocytic neoplasms are typically observed as encapsulated, solitary nodules often displaying a distinctive mahogany brown cut surface, sometimes featuring a central scar, resembling oncocytic lesions in other organs. While the majority of OCA measure over 3.0 cm, smaller tumors have been documented [5, 6, 53].

Intratumoral hemorrhage and infarction, which occasionally result from preoperative FNA procedures, are common findings in these neoplasms. On microscopic examination, the growth patterns of OCA can vary; solid and trabecular are the most prevalent. However, they can also exhibit microfollicular, macrofollicular, pseudopapillary, and, although rarely, true papillary structures. Notably, concentric calcifications resembling psammoma bodies may be present, and features such as intranuclear grooves and poorly formed intranuclear pseudo-inclusions can further complicate the diagnosis, especially when attempting to differentiate these oncocytic neoplasms from papillary thyroid carcinoma (PTC) [1, 3, 6].

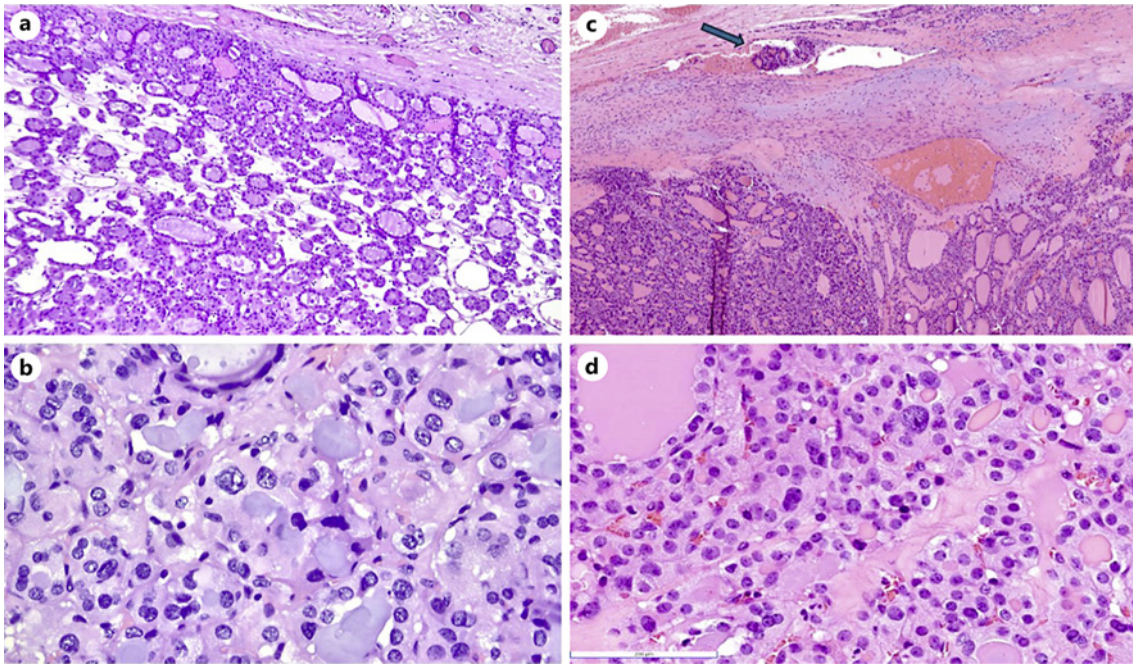

Fig. 3. Oncocytic adenoma (hematoxylin and eosin stain (**a**, **b**)). An encapsulated oncocytic neoplasm showing follicular growth pattern with random nuclear atypia and no evidence of invasive features. Oncocytic carcinoma (hematoxylin and eosin stain (**c**, **d**)). An encapsulated oncocytic tumor with follicular and solid growth pattern showing angioinvasion (arrow (**c**)) characterized by a tumor thrombus in a vessel lumen with tumor capsule attached to the vessel wall.

The classification of OCA hinges on the presence of invasive characteristics (Fig. 2). Specifically, the distinction between OA and OCA is made based on whether there is invasion of the tumor capsule and/or vascular invasion (angioinvasion) [3, 6, 11, 54]. Malignant behavior has not been consistently observed in cases diagnosed solely based on capsule invasion, leading to controversy over what constitutes significant capsular invasion. In clinical practice, adequately sampled cases defined by invasion into or through the tumor capsule can be classified as minimally invasive [11]. When vascular invasion occurs, particularly involving four or more vessels, the prognosis may be worse, indicating a higher risk for tumor recurrence and metastasis [2, 52, 54, 55]. Ultimately, widely invasive OCAs are more straightforward to diagnose due to their clear invasive characteristics into surrounding thyroid tissue and vascular structures [54–57]. Interestingly, in contrast to classic follicular carcinoma which spreads uniformly by hematogenous route, OCA can metastasize via both venous and lymphatic mechanisms. However, it has been shown that soft tissue deposits of OCA, once considered to represent completely replaced lymph nodes are nodular aggregates of OCA within vessels [58].

Cytomorphologic Features

If more than 75% of the cells in an aspirate are oncocytic follicular cells, it is classified as "follicular neoplasm with oncocytic features" (Bethesda category IV). These specimens typically show hypercellularity with oncocytic cells arranged in cohesive groups or sheets, with some follicle formation possible. Background colloid is usually scant or absent, though watery colloid may be noted, especially in macrofollicular cases [37, 59–61]. Random nuclear atypia can include nuclear enlargement, multinucleation, cellular pleomorphism, and prominent nucleoli in aspirates of oncocytic neoplasms [28, 29, 45]. Presence of intracytoplasmic holes or lumens and transgressing vessels among cell groups may be indicative of a neoplastic process compared to nonneoplastic oncocytic proliferations [62].

Some studies have shown that the cytomorphologic diagnosis of follicular neoplasm with oncocytic features carries a higher risk of malignancy as compared to cases without oncocytic features. However, this claim has been disputed by other authors. Table 1 highlights selected studies which report FNA specimens of oncocytic thyroid lesions and associated risks of malignancy [19, 63–71].

Oncocytic cell atypia, characterized by nuclear pleomorphism, hyperchromasia, and prominent nucleoli, has

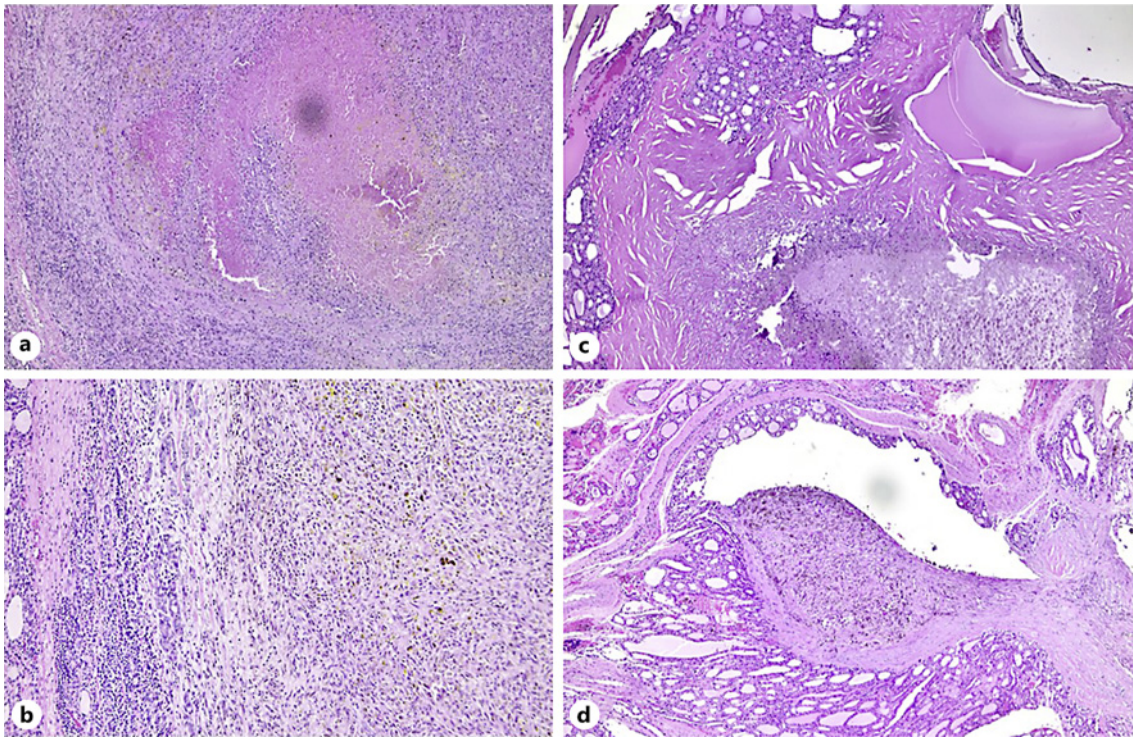

Fig. 4. Oncocytic neoplasm showing prominent post-FNA changes (hematoxylin and eosin stain (**a–d**)) consisting of near-total infarction (**a**), spindle cell proliferation (**b**), fibrosis and hemorrhage (**c**, **d**).

been considered as a useful indicator in FNA cytology for differentiating between benign and malignant oncocytic lesions (Fig. 2) [75]. However, it is important to note that atypical oncocytic cells are frequently observed in benign thyroid conditions, including adenomatoid nodules, especially those associated with chronic lymphocytic thyroiditis, as well as in diffuse toxic goiter, toxic nodular goiter, and dyshormonogenetic goiter [6, 10, 28]. This highlights the significance of considering the clinical context and the background pathology when interpreting cytological findings to avoid misdiagnosis of malignancy in cases where atypical oncocytic cells are present, particularly in lesions that are otherwise benign. In diagnostic practice, integrating cytological features with clinical presentation and imaging findings remains essential for accurate diagnosis and management.

Differentiated High-Grade and Poorly Differentiated OCA

The concept of poorly differentiated carcinoma is gaining clarity as we continue to parse apart differences from high-grade differentiated thyroid carcinoma. As the name suggests, poorly differentiated thyroid tumors do not retain the cytologic features of their precursor and must meet specific criteria set forth by the Turin doctrine [76]. In contrast, differentiated high-grade tumors retain cytomorphologic and architectural features of a prior well-differentiated tumor, which can include OCA. These histologically aggressive oncocytic tumors can create a challenge as they occasionally blur the line between these two entities. For example, OCA may exhibit a solid growth pattern. If sufficient proliferative activity is identified, a solid OCA may in fact meet the Turin criteria for a poorly differentiated neoplasm [3, 77, 78]. However, it must be noted that differentiated high-grade carcinoma can show foci of poorly differentiated histology, further muddying the waters between these two entities. In any event, both differentiated high-grade and poorly differentiated carcinoma portend poor prognosis and the distinction may be academic. Additionally, necrosis must be carefully evaluated as infarct-type necrosis, often seen in oncocytic neoplasms as mentioned above particularly following FNA, must not be used as criteria of one of these aggressive histologic variants. Rather true tumor necrosis with karyorrhectic debris must be present for this feature to be conclusively identified [2, 3].

Table 1. Selected studies with reported risk of malignancy in thyroid fine needle aspirates with oncocytic (Hürthle) cells

Study	#Cases	Surgical pathology F/U	% Malignant
Giorgadze et al. [63], 2004	206	169 (82%)	45
Pu et al. [66], 2006	87	87 (100%)	31
Zhang et al. [72], 2008	55	55 (100%)	16
Sippel et al. [73], 2008	57	57 (100%)	21
Sorrenti et al. [67], 2009	140	140 (100%)	18.6
Raparia et al. [68], 2009	37	37 (100%)	41
Kim et al. [74], 2010	57	57 (100%)	46
Strazisar et al. [19], 2010	279	279 (100%)	50
Keskek et al. [69], 2010	37	37 (100%)	22
Roh et al. [70], 2011	401	287 (71.6%)	24
Yazici et al. [71], 2016	39	39 (100%)	35.8
Agarwal et al. [65], 2019[a]	760	288 (38%)	12.8–33.7
Wong et al. [29], 2020	698	576 (82%)	27
Ren et al. [64], 2020	300	300	16

[a]Meta-analysis reporting risk of malignancy in low and high ranges.

It has been shown that only a subset (approximately 20%–30%) of FNA specimens from high-grade well-differentiated and poorly differentiated carcinomas exhibit diagnostic features, such as solid growth, tumor necrosis, and mitoses, sufficient to render a diagnosis or raise suspicion for these malignant tumors. In most series, these cases comprise around 10%–20% of FNA specimens and are classified as follicular neoplasms with oncocytic features [79–81].

Though distinct molecular features are not currently defined in the diagnosis of either differentiated high-grade or poorly differentiated carcinomas, it is likely that most of these aggressive neoplasms acquire molecular alterations during their evolution to promote adverse biologic behavior such as changes in *TP53* or *TERT* promoter, the latter of which can be associated with distant spread of tumor [82].

The Differential Diagnosis of Oncocytic Thyroid Neoplasm

Differential Diagnosis

As aforementioned, the differential diagnosis of an oncocytic thyroid neoplasm includes PTC subtypes with oncocytic features, oncocytic subtype of MTC, oncocytic lesions of the parathyroid gland, and metastatic tumors [6, 28, 83, 84].

PTC Subtypes with Oncocytic Features

PTC is indeed distinct among cancers due to its well-defined nuclear characteristics that are integral for diagnosis. These features, such as nuclear enlargement, chromatin clearing, and irregularities in the nuclear membrane, form the basis for identifying this malignancy in histopathological examinations [3, 85–88].

The following subtypes of PTC have their own unique characteristics including oncocytic features. Much like its namesake, the **Warthin-like PTC** shows papillae composed of cells with oncocytic cytoplasmic features and abundant lymphoplasmacytic inflammation. A diagnostic pitfall is the fact that these neoplasms often arise in conjunction with severe chronic lymphocytic thyroiditis, which can in and of itself lead to oncocytic metaplasia [89, 90]. Therefore, careful assessment must be made both at the time of FNA and during evaluation of surgical resection specimens for lymphocytic thyroiditis to discern a true neoplastic process from a reactive metaplasia. **Tall cell subtype of PTC** can also show cells with abundant eosinophilic cytoplasm. Though not perhaps meeting the exact criteria for oncocytic change as it is currently defined, we mention it here as this variant of PTC arises in the differential diagnosis, particularly in the rare instances of OCA with papillary architecture. As these tumors have been shown to clinically behave aggressively than other subtypes of PTC, in pathology specimens, a 30% threshold is

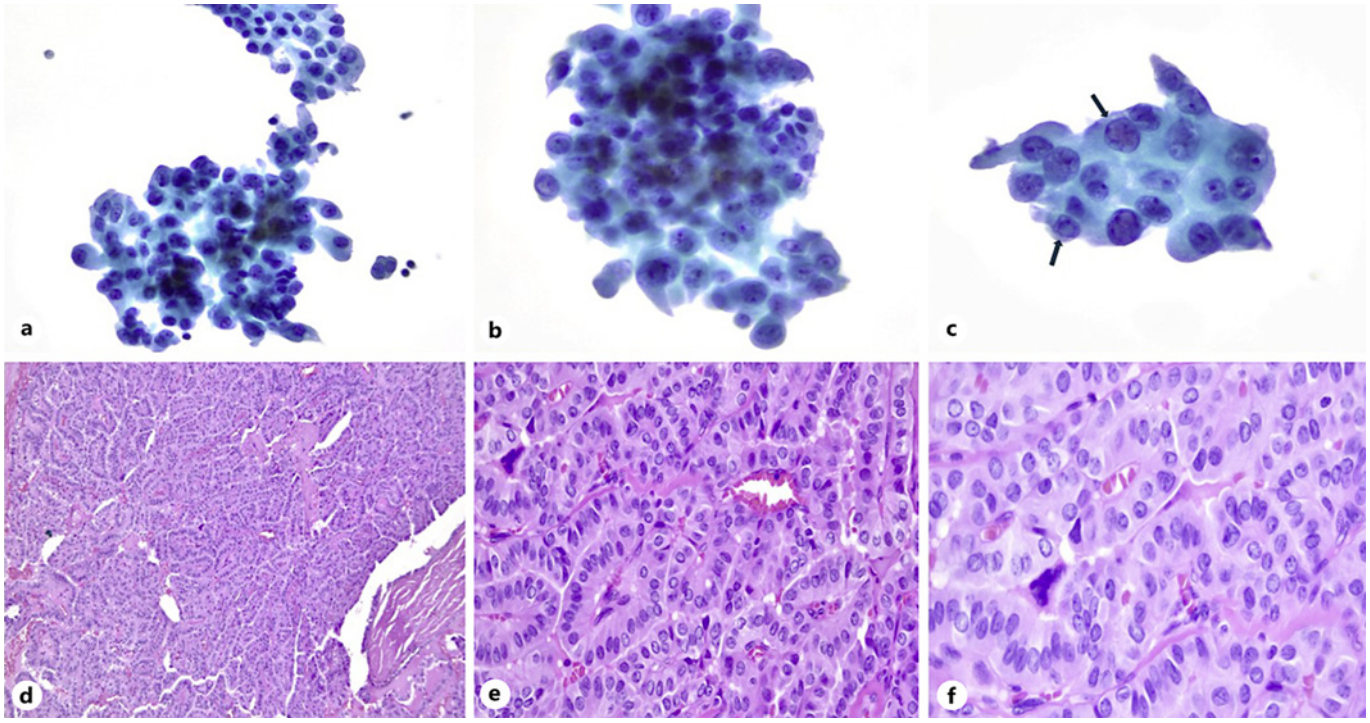

Fig. 5. Tall cell subtype of papillary thyroid carcinoma. The FNA specimen (alcohol-fixed smears, Papanicolaou stain (**a–c**)) showing elongated tumor cells with dense cytoplasm, and nuclear features of papillary thyroid carcinoma including intranuclear inclusion (arrow (**c**)). The histopathologic features (hematoxylin and eosin stain (**d–f**)) showing complex papillary architecture (**d**, **e**) and tall shaped (two-three times the width) tumor cells with oncocytic cytoplasm with nuclear features of papillary thyroid carcinoma (**f**).

required for the classification of the tall cell variant [3]. However, literature suggests that in cytology, the identification of tall cell features can be inconsistent and often unreliable. Preoperative assessments using FNA or CNB may fail to capture the true histological representation of the tumor, leading to discrepancies between cytological findings and follow-up histopathology. Given this limitation, treatment decisions should be made cautiously, as reliance on cytological or core biopsy findings alone may not accurately predict the potential of tumor's aggressiveness [91–93] (Fig. 5).

Oncocytic subtype of PTC is the least common and is characterized by its complex branching papillae and a predominance of oncocytic cells (greater than 75%) [3]. Despite its distinctive appearance, this subtype retains the nuclear features typical of PTC. Recent research indicates that while the oncocytic subtype tends to occur in an older demographic and often presents with larger tumor sizes, it does not significantly differ in terms of recurrence or disease-specific survival rates when compared to classic PTC (Coca-Pelaz, 2020 #436). This finding has been consistent across multiple studies, suggesting that despite the variability in presentation, the prognosis for patients with different variants may be more similar than previously thought [88, 94, 95].

Rare Oncocytic Subtype of Medullary Carcinoma

Unlike the other follicular-derived neoplasms covered in this review, MTC arises from the C cells of the thyroid. While some cases are sporadic, a significant proportion arise in association with inherited *RET* mutations as seen in multiple endocrine neoplasia type 2. Rarely, MTC can display an oncocytic pattern analogous to that seen in other oncocytic neoplasms which is why it must be noted in this review [96]. As such, it is prudent to keep this admittedly less common differential diagnosis in mind when one encounters a tumor with oncocytic morphology and take care to correlate the histopathologic findings with the patient's clinical history. If warranted, one may perform immunohistochemical staining for calcitonin to more definitively characterize such lesions [83, 96–99].

MTC is indeed distinct from other follicular-derived thyroid neoplasms, as it originates from the parafollicular C cells, which produce calcitonin. While many cases of

MTC occur sporadically, a notable portion is linked to germline mutations in the *RET* proto-oncogene, seen in hereditary syndromes like multiple endocrine neoplasia type 2. Given its potential oncocytic variant presentation, it is crucial for pathologists to be aware of MTC when evaluating tumors with oncocytic morphology. The oncocytic pattern in MTC, although less common, can pose diagnostic challenges and distinguishing it from other oncocytic tumors requires careful examination in both FNA and histopathology specimens. Correlating pathological findings with the patient's clinical history is essential. Immunohistochemical staining for calcitonin can be particularly valuable, as positive staining supports a diagnosis of MTC and helps differentiate it from other neoplasms exhibiting oncocytic features. In FNA cases lacking a cell block for immunostains, the diagnosis of MTC can be confirmed by assessment of calcitonin levels in blood or FNA rinse. Overall, a thorough and multifaceted diagnostic approach is critical to ensure accurate identification and management of this rare subtype of MTC [3, 83, 96, 97].

Oncocytic Change in Parathyroid Glands

While not emanating from thyroid parenchyma, the adjacent or intrathyroidal parathyroid glands can exhibit oncocytic change, a feature often seen in conjunction with normal aging [6, 35]. This finding can present a diagnostic dilemma, particularly in cases where on ultrasound a parathyroid lesion is mistaken for a thyroid nodule. In addition, at the time of frozen section should one be requested to assess the identity of a thyroid or thyroid-adjacent nodule, as such changes render a definitive diagnosis of parathyroid versus thyroid tissue quite difficult. Such cases may best be described as "oncocytic endocrine tissue, defer to permanent." At the time of FNA, a parathyroid lesion can be confirmed by performing PTH level assessment of FNA rinse (Fig. 6). If necessary, immunostains for PAX8, TTF1, thyroglobulin, and PTH may be helpful in confirming parathyroid origin in both cell block and histopathologic specimens. This oncocytic change may be focal or more widespread; in the latter situation, the term oncocytic/oxyphilic adenoma may be used. Of clinical relevance, such oncocytic parathyroid adenomas tend to be larger and more symptomatic than non-oncocytic lesions [34, 35, 100].

Molecular Profile of Oncocytic Neoplasms

The classification of molecular changes in OCA has indeed been an area of growing research interest, helping elucidate its distinct characteristics compared to other thyroid cancers such as follicular carcinoma and PTC [101]. Table 2 highlights the key morphologic features and molecular profiles of oncocytic thyroid lesions. The molecular profiles of OCAs typically involve at least some of the following:

Complex I Mutations

Most mitochondrial DNA mutations in OCAs are associated with genes encoding complex I of the mitochondrial respiratory chain. This complex comprises seven hydrophobic subunits (*ND1*, *ND2*, *ND3*, *ND4*, *ND4L*, *ND5*, *ND6*), all of which have been found to be mutated in OCA, albeit at varying frequencies. Among the *ND* genes, studies, such as those by Gopal et al. [102], demonstrate that *ND5* is the most commonly mutated, followed by *ND2*, *ND4*, and *ND1*. These mutations contribute to the altered energy metabolism characteristic of oncocytic cells found in OCA. Besides the *ND* genes, other mitochondrial genes have also been identified with mutations, including *CO1*, *CO2*, *CO3*, *CYB*, and *ATP6*. These mutations have been observed consistently across different studies, indicating a recurrent pattern that may be significant for OCA. Mitochondrial DNA mutations are not exclusive to oncocytic neoplasms. Similar mutations have been documented in other thyroid malignancies, such as papillary and follicular thyroid carcinomas, as well as in various other cancers. This suggests that while mitochondrial mutations may be involved in the pathogenesis of OCA, they are part of a broader oncogenic process present in multiple tumor types. The concept of a common deletion in mitochondrial DNA, originally thought to be prevalent in oncocytic neoplasms, specifically between nucleotides 8,470 and 13,447, has been contested by recent studies that found no significant association in oncocytic neoplasms compared to other malignancies. The understanding of mitochondrial DNA mutations in OCA underscores the complex interplay between energy metabolism and tumorigenesis. These disruptive mutations, particularly in complex I subunit genes, not only provide insights into the unique biology of OCA but also highlight the need for further research to understand their role in tumor progression and potential therapeutic implications [27, 103].

Chromosomal Abnormalities Associated with OCA

Corver et al. [104, 105] were pioneers in identifying the near-haploid genome characteristic of OCA, distinguishing it from the karyotypes observed in papillary and follicular thyroid carcinomas. This unique genetic configuration highlights the distinct biological behavior of these tumors. During the analysis of OCAs, it was found that chromosome 7 consistently retains a heterozygous status. In subsequent studies by Ganly et al. [106] and Gopal et al. [102], the presence of additional copies of chromosome 7 was noted,

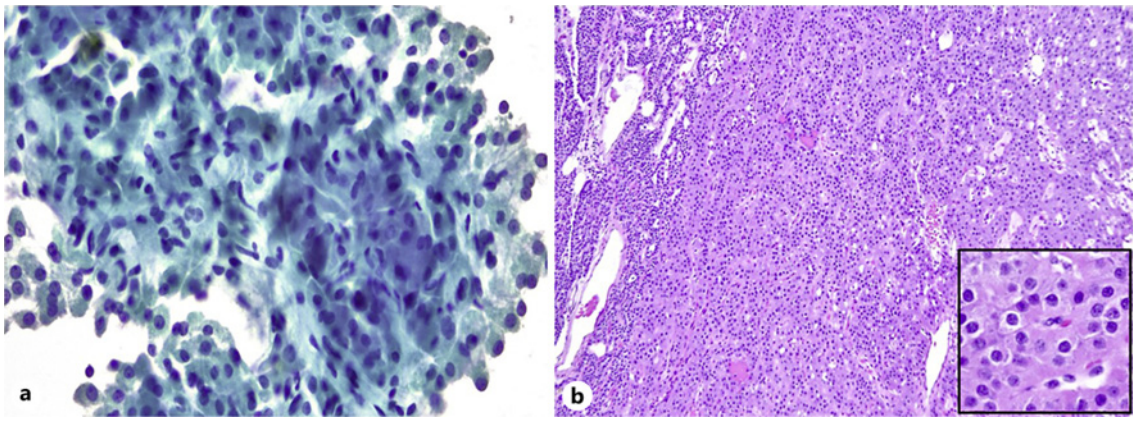

Fig. 6. Oncocytic adenoma of parathyroid gland. The FNA specimen showing a cohesive group of oncocytic cells (alcohol-fixed smear, Papanicolaou stain) (**a**). The histopathology (hematoxylin and eosin stain) shows an oncocytic neoplasm (inset (**b**)) with an associated rim of normocellular parathyroid tissue.

attributed to genome-wide duplication events, leading to loss of heterozygosity in other haploid chromosomes. Notably, chromosome 7 harbors the *BRAF* gene, and the proliferation of this chromosome could facilitate gene amplification and overexpression, impacting tumorigenesis. Apart from chromosome 7, chromosomes 5 and 12 also frequently maintained a heterozygous state, with instances of additional copies, possibly contributing to the tumor's complexity and behavior. Corver et al. [104, 105] also suggested that the near-haploid genome may be driven by reactive oxygen species (ROS), produced due to mitochondrial DNA mutations in components of the respiratory chain. These mutations are associated with a shift toward a glycolysis-dependent metabolism, leading to further accumulation of ROS which can perturb genomic stability [104, 105].

Both the near-haploid genome and mitochondrial DNA mutations have been identified as early (truncal) events in the evolution of OCA. These genetic changes are not only present in primary tumors but are also shared in recurrences and metastases, highlighting their potential roles in the progression and persistence of the disease. The association of a near-haploid genome with OCA underscores the tumor's unique genetic landscape, with implications for understanding its pathophysiology and potential therapeutic targets. The interplay between mitochondrial dysfunction, oxidative stress, and chromosomal alterations provides a rich area for ongoing research, aiming to unveil the mechanisms driving oncocytic thyroid malignancy and identifies strategies for intervention. Mitochondrial mutations in these tumors lead to impaired oxidative phosphorylation, resulting in reduced ATP production and a compensatory shift toward glycolysis, a phenomenon known as the Warburg effect. This metabolic adaptation contributes to increased ROS levels, which in turn drive genomic instability, promoting chromosomal alterations and tumor progression. Beyond fueling tumor growth, these metabolic changes also shape the tumor microenvironment, potentially influencing therapeutic responses [24, 82].

Mutations in Nuclear DNA OCA

The *TERT* promoter mutation is notably frequent in OCA, with reported prevalence ranging from 13% to 32% across multiple studies. However, *TERT* promoter mutations are indeed prominent in OCA, and they also occur in other aggressive thyroid malignancies, suggesting that this mutation may not be unique to this malignant tumor. Minimally invasive and low-risk OCAs are less likely to harbor *TERT* promoter mutations compared to widely invasive or angioinvasive types. However, *TERT* promoter mutations found in minimally invasive cases are associated with focal angioinvasion. It has been shown that mutations in OCA tend to cluster in specific cellular pathways, particularly signaling pathways and tumor suppressor pathways. Notably, mutations in the MAPK and mTOR signaling pathways were identified in approximately 55% of cases. Key genes in this context include *EGFR*, *EIF1AX*, *ERBB2*, *MET*, *NF1*, *PDGFR*, *PTEN*, *RAS*, *RET*, *TSC1/2*, and *TSHR*. [24, 50, 107–109].

Mutations in genes related to DNA damage and repair have also been identified in OCA including *ATM*, *BRCA1*, *CDKN1A*, *CHEK2*, *RB1*, *TP53*, and others involved in the DNA repair mechanisms. A significant percentage of OCAs cases display mutations associated with epigenetic modifications, including *ARID1A*, *CREBBP*, *DNMT1*, *EZH1*, *KMT2C*, *SWI/SNF*, and genes, among others.

Table 2. Key pathologic and molecular features of oncocytic thyroid lesions

	Cytomorphologic features	Histopathologic features	Molecular findings
Adenomatous oncocytic nodule	• Predominance of oncocytic cells • Limited population of benign appearing follicular cells Background watery colloid • Often classified as TBSRTC category III and rarely IV	• Multiple oncocytic nodules scattered throughout normal thyroid parenchyma lacking a well-developed capsule • Can show changes related to preoperative FNA	• No specific findings
Oncocytic adenoma	• >75% oncocytic cells in cohesive groups/sheets, possible follicle formation • Intracytoplasmic lumens and transgressing vessels • Random cellular atypia • Scant or lack of watery colloid • Often classified as TBSRTC IV	• Discrete oncocytic nodule with well-demarcated tumor capsule • Lack of capsular invasion or angioinvasion • Can show changes related to preoperative FNA	• Mutations in mitochondrial complex 1 subunit genes, *GRIM-19*, *RAS*, *EIF1AX* • Copy number alterations – rare
Oncocytic carcinoma	• Cytomorphology like oncocytic adenoma • Often classified as TBSRTC IV	• Discrete cellular oncocytic tumor in solid, trabecular, microfollicular, macrofollicular, pseudopapillary, or true papillary architecture with or without psammoma bodies • Presence of either tumor capsule invasion (either minimal or extensive) and/or angioinvasion • Can show changes related to preoperative FNA	• Mutations in mitochondrial complex 1 subunit genes (*ND1-6*), *CO1-3*, *CYB*, *ATP6*, *RAS*, *EIF1AX* • *TERT* promoter, MAP-kinase and mTOR signaling pathway alterations (*EIF1AX, NF1*, *PTEN*, *TSC1/2*, *RAS*, *EGFR*, *ERBB2*, *PDGFR*, *TSHR*, *MET*, and *RET*) • DNA damage and repair pathways (*ATM*, *TP53*, *CHEK2*, *CDKN1A*, *RB1*, *BRCA1*) • Epigenetic pathways (*SWI/SNF*, *ARID1A*, *CREBBP*, *KMT2C*, *EZH1*, and *DNMT1*) • Presence of copy number alterations including polysomy 7, possible gain of chromosome 5 and 12
Differentiated high-grade/poorly differentiated carcinoma	• Cytomorphology like oncocytic adenoma • Often classified as TBSRTC IV • Potential necrosis or mitotic activity can be found and will lead to a diagnosis of TBSRTC V but is not always present on FNA due to sampling	• Solid oncocytic neoplasm with tumor necrosis and/or mitotic activity	• *TP53* or *TERT* promoter mutations are common
Papillary thyroid carcinoma	• Monomorphic cell population arranged in papillary structures with nuclear features of papillary thyroid carcinoma, including pseudo-inclusions and clear powdery chromatin • Often classified as TBSRTC V or VI	• Papillary structures with true fibrovascular cores • Presence of readily identifiable nuclear features of papillary carcinoma • Scattered psammomatous calcifications • Warthin-like papillary thyroid carcinoma shows abundant lymphoplasmacytic infiltrates within the stroma of papillae • Oncocytic subtype shows >75% oncocytic change with nuclear features of papillary thyroid carcinoma	• *BRAF or RAS* mutations • *RET* fusions

Table 2 (continued)

	Cytomorphologic features	Histopathologic features	Molecular findings
Medullary thyroid carcinoma, oncocytic	• Spindled or plasmacytoid cells • "Stippled nuclear chromatin" • Prominent nucleoli, focal • Acellular deposits of amyloid with or without associated cells • Elevated calcitonin levels in serum or FNA rinse	• Spindled or nested architecture with oncocytic change • Stromal amyloid may be present	• *RET* mutations • *RAS* mutations

TBSRTC, The Bethesda System for Reporting Thyroid Cytology; FNA, fine needle aspiration.

Mutations in genes playing a vital role in angiogenesis have also been reported in a subset of OCAs [24, 39, 40, 51, 54, 110–112].

The complex mutational landscape of OCA not only elucidates the tumorigenic processes underlying its pathogenesis but also highlights potential avenues for targeted therapies and further research into its biological behavior and clinical outcomes [101]. Understanding these mutations could facilitate the stratification of patients and the development of personalized treatment approaches in the context of aggressive thyroid cancers [39, 40, 110].

OAs: Molecular Features and Distinctions from Carcinomas

OAs share molecular features with OCAs but with some distinct characteristics. These benign tumors frequently harbor mitochondrial DNA mutations, particularly in Complex I genes, yet lack the extensive chromosomal losses and near-haploidy seen in OCAs, they may display random chromosomal gains, especially involving chromosome 7, and less frequently, losses on chromosome 22. *RAS* mutations have been identified in a subset of cases, though at a lower frequency than in carcinomas. Overall, OAs exhibit a less complex molecular profile, with fewer high-risk alterations and lower frequencies of *TERT* and *TP53* mutations. While mitochondrial abnormalities are common in both adenomas and carcinomas, the genomic stability and absence of widespread chromosomal imbalances in adenomas suggest that mitochondrial dysfunction alone is not necessarily indicative of malignancy [49, 102, 106].

Molecular Testing of Cytologically Indeterminate Oncocytic Lesions

The differentiation between benign and malignant oncocytic lesions, particularly in the context of thyroid FNA, can be challenging due to overlapping cytomorphologic characteristics. As mentioned above, oncocytic thyroid lesions or those containing variable proportions of oncocytic cells may cause diagnostic conundrums.

To address the limitations of traditional cytological evaluation, the integration of adjunct molecular tests has emerged as a valuable strategy. These tests often assess genetic mutations, gene expression profiles, or other molecular markers that can enhance diagnostic accuracy and provide additional information regarding the potential for malignancy and clinical risk stratification. By utilizing these molecular tools in conjunction with traditional cytological assessment, clinicians can reduce the rate of unnecessary surgeries for benign lesions and improve patient management through more accurate risk stratification. As the field continues to evolve, ongoing research is expected to further refine these molecular diagnostics and enhance their clinical utility in the evaluation of oncocytic thyroid lesions [113–118]. Some of the commercially available molecular tests for indeterminate thyroid FNA specimens include the following:

ThyroSeq®

A next-generation sequencing panel that analyzes multiple genes associated with thyroid cancer, helping clarify the risk of malignancy in indeterminate cases. The current third iteration of the ThyroSeq® panel demonstrates advancements in its ability to detect genetic alterations that can indicate the likelihood of malignancy in these indeterminate cases. Over the years, ThyroSeq® has shown improvements in the classification of oncocytic thyroid lesions as compared to its prior version. It has been shown that the most frequent alteration in oncocytic thyroid lesions classified as TBSRTC III or IV show copy number alteration alone and *RAS* (*KRAS* and *NRAS*) mutations [60, 114, 115, 119, 120].

Afirma®

This sequencing-based test evaluates the gene expression of specific markers to classify indeterminate thyroid nodules as benign or suspicious for malignancy. Its earlier version known as Afirma® Gene Expression Classifier (GEC) showed low predictive value for oncocytic thyroid lesions [121, 122]. However, its recent version Afirma® Genomic Sequencing Classifier (GSC) has been designed to improve upon the predictive capabilities of the GEC, especially for oncocytic thyroid lesions, which showed lower predictive value in previous assessments. This improvement allows for better differentiation between benign and malignant nodules [123–128].

Other commercially available molecular tests, such as *RosettaGX Reveal (miRNA)*®, *ThyGeNEXT*®*/ThyraMIR*®, and *ThyroidPRINT*®, along with multigene expression panels, have shown potential in enhancing the predictive value of indeterminate oncocytic thyroid FNA specimens. However, there is currently insufficient data in the literature, particularly for oncocytic lesions, to draw definitive conclusions [118, 129–132].

Conclusion

Overall, oncocytic thyroid tumors are relatively uncommon, but it is crucial to accurately identify them due to their distinct histopathological, molecular, and clinical characteristics. These tumors, though rare, can present diagnostic challenges and must be carefully differentiated from other more prevalent thyroid lesions, as misdiagnosis could impact clinical management and treatment decisions. In the process of distinguishing oncocytic lesions from other thyroid pathologies, it is also important to consider the involvement of nearby endocrine structures, particularly the parathyroid glands. Such scenarios can lead to diagnostic conundrums, especially when the specimen's cellularity is limited, such as FNA biopsies. In such cases, the cellular composition may not be sufficient to draw clear conclusions. The ability to recognize these subtle nuances ensures a more accurate diagnosis and guides appropriate management strategies for patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.A.G. wrote the initial draft of the manuscript and edited subsequent versions. Z.W.B. and S.C. conceived the idea for the manuscript, edited drafts, created figures, and approved the finalized version as well as created figures.

References

1 Jalaly JB, Baloch ZW. Hurthle-cell neoplasms of the thyroid: an algorithmic approach to pathologic diagnosis in light of molecular advances. Semin Diagn Pathol. 2020;37(5):234–42. https://doi.org/10.1053/j.semdp.2020.03.004

2 Christofer Juhlin C, Mete O, Baloch ZW. The 2022 WHO classification of thyroid tumors: novel concepts in nomenclature and grading. Endocr Relat Cancer. 2023;30(2):e220293. https://doi.org/10.1530/ERC-22-0293

3 Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO classification of thyroid neoplasms. Endocr Pathol. 2022;33(1):27–63. https://doi.org/10.1007/s12022-022-09707-3

4 Nesland JM, Sobrinho-Simões MA, Holm R, Sambade MC, Johannessen JV. Hurthle-cell lesions of the thyroid: a combined study using transmission electron microscopy, scanning electron microscopy, and immunocytochemistry. Ultrastruct Pathol. 1985;8(4):269–90. https://doi.org/10.3109/01913128509141518

5 Asa SL, Mete O. Oncocytic change in thyroid pathology. Front Endocrinol. 2021;12:678119. https://doi.org/10.3389/fendo.2021.678119

6 Canberk S, LiVolsi VA, Baloch Z. Oncocytic lesions of the neuroendocrine system. Adv Anat Pathol. 2014;21(2):69–82. https://doi.org/10.1097/PAP.0000000000000011

7 Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hurthle (oncocytic) cell and its associated pathologic conditions: a surgical pathology and cytopathology review. Arch Pathol Lab Med. 2008;132(8):1241–50. https://doi.org/10.5858/2008-132-1241-TTHOCA

8 Mete O, Asa SL. Oncocytes, oxyphils, Hurthle, and Askanazy cells: morphological and molecular features of oncocytic thyroid nodules. Endocr Pathol. 2010;21(1):16–24. https://doi.org/10.1007/s12022-009-9102-2

9 Baloch ZW, LiVolsi VA. Oncocytic lesions of the neuroendocrine system. Semin Diagn Pathol. 1999;16(2):190–9.

10 Canberk S, Griffin AC, Goyal A, Wang H, Montone K, Livolsi V, et al. Oncocytic follicular nodules of the thyroid with or without chronic lymphocytic thyroiditis: an institutional experience. CytoJournal. 2013;10:2. https://doi.org/10.4103/1742-6413.106686

11 Stegenga MT, Oudijk L, van Velsen EFS, Peeters RP, Medici M, Verburg FA, et al. Impact of reclassification of oncocytic and follicular thyroid carcinoma by the 2022 WHO classification. J Clin Endocrinol Metab. 2024:dgae581. https://doi.org/10.1210/clinem/dgae581

12 DeLellis RA. In: Kleihues P, Sobin LE, editors. WHO: Pathology and genetics. Tumours of endocrine organs. WHO classification of tumours. Lyon, France: IARC Press; 2004.

13 WHO Classification of Tumours of Endocrine Organs. WHO/IARC classification of tumours. 4th 10th ed. Lyon, France: WHO/IARC Press; 2017.
14 Gundry SR, Burney RE, Thompson NW, Lloyd R. Total thyroidectomy for Hurthle cell neoplasm of the thyroid. Arch Surg. 1983;118(5):529–32. https://doi.org/10.1001/archsurg.1983.01390050013002
15 McLeod MK, Thompson NW. Hurthle cell neoplasms of the thyroid. Otolaryngol Clin North Am. 1990;23(3):441–52. https://doi.org/10.1016/s0030-6665(20)31268-8
16 Thompson NW, Dunn EL, Batsakis JG, Nishiyama RH. Hurthle cell lesions of the thyroid gland. Surg Gynecol Obstet. 1974;139(4):555–60.
17 Stojadinovic A, Ghossein RA, Hoos A, Urist MJ, Spiro RH, Shah JP, et al. Hurthle cell carcinoma: a critical histopathologic appraisal. J Clin Oncol. 2001;19(10):2616–25. https://doi.org/10.1200/JCO.2001.19.10.2616
18 Stojadinovic A, Hoos A, Ghossein RA, Urist MJ, Leung DHY, Spiro RH, et al. Hurthle cell carcinoma: a 60-year experience. Ann Surg Oncol. 2002;9(2):197–203. https://doi.org/10.1007/BF02557374
19 Strazisar B, Petric R, Sesek M, Zgajnar J, Hocevar M, Besic N. Predictive factors of carcinoma in 279 patients with Hurthle cell neoplasm of the thyroid gland. J Surg Oncol. 2010;101(7):582–6. https://doi.org/10.1002/jso.21526
20 Tallini G. Oncocytic tumours. Virchows Arch. 1998;433(1):5–12. https://doi.org/10.1007/s004280050209
21 Tallini G, Carcangiu ML, Rosai J. Oncocytic neoplasms of the thyroid gland. Acta Pathol Jpn. 1992;42(5):305–15. https://doi.org/10.1111/j.1440-1827.1992.tb02879.x
22 Poller DN, Megadmi H, Ward MJA, Trimboli P. Hurthle cells on fine-needle aspiration cytology are important for risk assessment of focally PET/CT FDG avid thyroid nodules. Cancers. 2020;12(12):3544. https://doi.org/10.3390/cancers12123544
23 Goffredo P, Roman SA, Sosa JA. Hurthle cell carcinoma: a population-level analysis of 3311 patients. Cancer. 2013;119(3):504–11. https://doi.org/10.1002/cncr.27770
24 Bischoff LA, Ganly I, Fugazzola L, Buczek E, Faquin WC, Haugen BR, et al. Molecular alterations and comprehensive clinical management of oncocytic thyroid carcinoma: a review and multidisciplinary 2023 update. JAMA Otolaryngol Head Neck Surg. 2024;150(3):265–72. https://doi.org/10.1001/jamaoto.2023.4323
25 Maximo V, Soares P, Lima J, Cameselle-Teijeiro J, Sobrinho-Simões M. Mitochondrial DNA somatic mutations (point mutations and large deletions) and mitochondrial DNA variants in human thyroid pathology: a study with emphasis on Hurthle cell tumors. Am J Pathol. 2002;160(5):1857–65. https://doi.org/10.1016/S0002-9440(10)61132-7
26 Maximo V, Botelho T, Capela J, Soares P, Lima J, Taveira A, et al. Somatic and germline mutation in GRIM-19, a dual function gene involved in mitochondrial metabolism and cell death, is linked to mitochondrion-rich (Hurthle cell) tumours of the thyroid. Br J Cancer. 2005;92(10):1892–8. https://doi.org/10.1038/sj.bjc.6602547
27 Gopal RK, Vantaku VR, Panda A, Reimer B, Rath S, To TL, et al. Effectors enabling adaptation to mitochondrial complex I loss in hurthle cell carcinoma. Cancer Discov. 2023;13(8):1904–21. https://doi.org/10.1158/2159-8290.CD-22-0976
28 Thodou E, Canberk S, Schmitt F. Challenges in cytology specimens with hurthle cells. Front Endocrinol. 2021;12:701877. https://doi.org/10.3389/fendo.2021.701877
29 Wong KS, Jo VY, Lowe AC, Faquin WC, Renshaw AA, Shah AA, et al. Malignancy risk for solitary and multiple nodules in Hurthle cell-predominant thyroid fine-needle aspirations: a multi-institutional study. Cancer Cytopathol. 2020;128(1):68–75. https://doi.org/10.1002/cncy.22213
30 Yang GC, Schreiner AM, Sun W. Can abundant colloid exclude oncocytic (Hurthle cell) carcinoma in thyroid fine needle aspiration? Cytohistological correlation of 127 oncocytic (Hurthle cell) lesions. Cytopathology. 2013;24(3):185–93. https://doi.org/10.1111/j.1365-2303.2012.00988.x
31 Mijovic T, Rochon L, Gologan O, Hier MP, Black MJ, Young J, et al. Fine-needle aspiration biopsies in the management of indeterminate follicular and Hurthle cell thyroid lesions. Otolaryngol Head Neck Surg. 2009;140(5):715–9. https://doi.org/10.1016/j.otohns.2009.01.022
32 Wu HH, Clouse J, Ren R. Fine-needle aspiration cytology of Hurthle cell carcinoma of the thyroid. Diagn Cytopathol. 2008;36(3):149–54. https://doi.org/10.1002/dc.20750
33 Gonzalez JL, Wang HH, Ducatman BS. Fine-needle aspiration of Hurthle cell lesions. A cytomorphologic approach to diagnosis. Am J Clin Pathol. 1993;100(3):231–5. https://doi.org/10.1093/ajcp/100.3.231
34 Howson P, Kruijff S, Aniss A, Pennington T, Gill AJ, Dodds T, et al. Oxyphil cell parathyroid adenomas causing primary hyperparathyroidism: a clinico-pathological correlation. Endocr Pathol. 2015;26(3):250–4. https://doi.org/10.1007/s12022-015-9378-3
35 Giorgadze T, Stratton B, Baloch ZW, Livolsi VA. Oncocytic parathyroid adenoma: problem in cytological diagnosis. Diagn Cytopathol. 2004;31(4):276–80. https://doi.org/10.1002/dc.20115
36 Paker I, Yilmazer D, Yandakci K, Arikok AT, Alper M. Intrathyroidal oncocytic parathyroid adenoma: a diagnostic pitfall on fine-needle aspiration. Diagn Cytopathol. 2010;38(11):833–6. https://doi.org/10.1002/dc.21338
37 Rossi ED, Baloch Z. The impact of the 2022 WHO classification of thyroid neoplasms on everyday practice of cytopathology. Endocr Pathol. 2023;34(1):23–33. https://doi.org/10.1007/s12022-023-09756-2
38 Suster D, Ronen N, Giorgadze T. Oncocytic nodular hyperplasia of the thyroid. Ann Diagn Pathol. 2022;61:152049. https://doi.org/10.1016/j.anndiagpath.2022.152049
39 Landau MS, Nikiforov YE, Ohori NP, Chiosea SI. Impact of molecular testing on detecting mimics of oncocytic neoplasms in thyroid fine-needle aspirates diagnosed as follicular neoplasm of Hurthle cell (oncocytic) type. Cancer Cytopathol. 2021;129(10):788–97. https://doi.org/10.1002/cncy.22439
40 Gilani SM, Ross JA, Prasad ML, Hammers L, Cai G, Adeniran AJ. Molecular alterations in Hurthle cell neoplasms of thyroid: a fine needle aspiration cytology study with cytology-histology correlation. Cancer Cytopathol. 2021;129(5):363–73. https://doi.org/10.1002/cncy.22370
41 Andrianus S, Gubbiotti MA, Mandel SJ, Nikiforov YE, Baloch Z. Unraveling the significance of TSHR mutations in indeterminate thyroid cytology specimens. Diagn Cytopathol. 2023;51(7):406–13. https://doi.org/10.1002/dc.25138
42 Lee SK, Rho BH, Woo SK. Hurthle cell neoplasm: correlation of gray-scale and power Doppler sonographic findings with gross pathology. J Clin Ultrasound. 2010;38(4):169–76. https://doi.org/10.1002/jcu.20684
43 Spagnuolo GM, Tierney HT, Laver NMV, Eldeiry LS. A retrospective study of clinicopathologic outcomes of nodules with hurthle cell cytology and the thyroid nodule app (TNAPP) ultrasound recommendations. Endocr Pract. 2022;28(6):593–8. https://doi.org/10.1016/j.eprac.2022.03.011
44 Nikiforova MN, Mercurio S, Wald AI, Barbi de Moura M, Callenberg K, Santana-Santos L, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. Cancer. 2018;124(8):1682–90. https://doi.org/10.1002/cncr.31245
45 Wong KS, Angell TE, Barletta JA, Krane JF. Hurthle cell lesions of the thyroid: progress made and challenges remaining. Cancer Cytopathol. 2021;129(5):347–62. https://doi.org/10.1002/cncy.22375
46 Li S, Baloch ZW, Tomaszewski JE, LiVolsi VA. Worrisome histologic alterations following fine-needle aspiration of benign parotid lesions. Arch Pathol Lab Med. 2000;124(1):87–91. https://doi.org/10.5858/2000-124-0087-WHAFFN
47 LiVolsi VA, Merino MJ. Worrisome histologic alterations following fine-needle aspiration of the thyroid (WHAFFT). Pathol Annu. 1994;29 (Pt 2)(Pt 2):99–120.

48 Bonora E, Porcelli AM, Gasparre G, Biondi A, Ghelli A, Carelli V, et al. Defective oxidative phosphorylation in thyroid oncocytic carcinoma is associated with pathogenic mitochondrial DNA mutations affecting complexes I and III. Cancer Res. 2006; 66(12):6087–96. https://doi.org/10.1158/0008-5472.CAN-06-0171
49 Gasparre G, Porcelli AM, Bonora E, Pennisi LF, Toller M, Iommarini L, et al. Disruptive mitochondrial DNA mutations in complex I subunits are markers of oncocytic phenotype in thyroid tumors. Proc Natl Acad Sci U S A. 2007;104(21):9001–6. https://doi.org/10.1073/pnas.0703056104
50 Doerfler WR, Nikitski AV, Morariu EM, Ohori NP, Chiosea SI, Landau MS, et al. Molecular alterations in Hurthle cell nodules and preoperative cancer risk. Endocr Relat Cancer. 2021;28(5):301–9. https://doi.org/10.1530/ERC-20-0435
51 Kure S, Ohashi R. Thyroid hurthle cell carcinoma: clinical, pathological, and molecular features. Cancers. 2020;13(1):26. https://doi.org/10.3390/cancers13010026
52 Fariduddin MM, Mathias PM, Syed W. Hurthle cell thyroid carcinoma. StatPearls. Treasure Island (FL); 2024.
53 Sobrinho-Simoes MA, Nesland JM, Holm R, Sambade MC, Johannessen JV. Hurthle cell and mitochondrion-rich papillary carcinomas of the thyroid gland: an ultrastructural and immunocytochemical study. Ultrastruct Pathol. 1985;8(2–3):131–42. https://doi.org/10.3109/01913128509142147
54 Sherman S. Oncocytic (hurthle cell) thyroid carcinoma. StatPearls. Treasure Island (FL); 2025.
55 Gruszczynski NR, Hasan SS, Brennan AG, De La Chapa J, Reddy AS, Martin DN, et al. Oncocytic carcinoma of the thyroid: conclusions from a 20-year patient cohort. Head Neck. 2024;46(8):2042–7. https://doi.org/10.1002/hed.27700
56 Fariduddin MM, Syed W. Hurthle cell thyroid carcinoma. StatPearls. Treasure Island (FL); 2021.
57 Zhou X, Zheng Z, Chen C, Zhao B, Cao H, Li T, et al. Clinical characteristics and prognostic factors of Hurthle cell carcinoma: a population based study. BMC Cancer. 2020; 20(1):407. https://doi.org/10.1186/s12885-020-06915-0
58 Bishop JA, Wu G, Tufano RP, Westra WH. Histological patterns of locoregional recurrence in Hurthle cell carcinoma of the thyroid gland. Thyroid. 2012;22(7):690–4. https://doi.org/10.1089/thy.2011.0407
59 Doghri R, Znaidi N, Blel A, Aloui R, Lahyeni R, Ben Salah M, et al. Thyroid oncocytic neoplasms. Tunis Med. 2018;96(3):219–23.
60 Geetha SD, Karam P, Ziemba Y, Chau K, Savant D, Rosca O, et al. Correlation of cytologic features with molecular testing of indeterminate oncocytic (hurthle cell) thyroid lesions. Diagn Cytopathol. 2025;53(3): 102–10. https://doi.org/10.1002/dc.25424
61 Yang GC, Schreiner AM, Sun W. Can abundant colloid exclude oncocytic (Hurthle cell) carcinoma in thyroid fine needle aspiration? Cytohistological correlation of 127 oncocytic (Hurthle cell) lesions. Cytopathology. 2013;24(3):185–93. https://doi.org/10.1111/j.1365-2303.2012.00988.x
62 Yang YJ, Khurana KK. Diagnostic utility of intracytoplasmic lumen and transgressing vessels in evaluation of Hurthle cell lesions by fine-needle aspiration. Arch Pathol Lab Med. 2001;125(8):1031–5. https://doi.org/10.5858/2001-125-1031-DUOILA
63 Giorgadze T, Rossi ED, Fadda G, Gupta PK, Livolsi VA, Baloch Z. Does the fine-needle aspiration diagnosis of "Hurthle-cell neoplasm/follicular neoplasm with oncocytic features" denote increased risk of malignancy? Diagn Cytopathol. 2004;31(5): 307–12. https://doi.org/10.1002/dc.20132
64 Ren Y, Kyriazidis N, Faquin WC, Soylu S, Kamani D, Saade R, et al. The presence of hurthle cells does not increase the risk of malignancy in most Bethesda categories in thyroid fine-needle aspirates. Thyroid. 2020; 30(3):425–31. https://doi.org/10.1089/thy.2019.0190
65 Agarwal S, Bychkov A, Jung CK, Hirokawa M, Lai CR, Hong S, et al. The prevalence and surgical outcomes of Hurthle cell lesions in FNAs of the thyroid: a multi-institutional study in 6 Asian countries. Cancer Cytopathol. 2019;127(3):181–91. https://doi.org/10.1002/cncy.22101
66 Pu RT, Yang J, Wasserman PG, Bhuiya T, Griffith KA, Michael CW. Does Hurthle cell lesion/neoplasm predict malignancy more than follicular lesion/neoplasm on thyroid fine-needle aspiration? Diagn Cytopathol. 2006; 34(5):330–4. https://doi.org/10.1002/dc.20440
67 Sorrenti S, Trimboli P, Catania A, Ulisse S, De Antoni E, D'Armiento M. Comparison of malignancy rate in thyroid nodules with cytology of indeterminate follicular or indeterminate Hurthle cell neoplasm. Thyroid. 2009;19(4):355–60. https://doi.org/10.1089/thy.2008.0338
68 Raparia K, Min SK, Mody DR, Anton R, Amrikachi M. Clinical outcomes for "suspicious" category in thyroid fine-needle aspiration biopsy: patient's sex and nodule size are possible predictors of malignancy. Arch Pathol Lab Med. 2009;133(5):787–90. https://doi.org/10.5858/133.5.787
69 Keskek M, Ocak S, Ozalp N, Koc M, Tez M. Clinical significance of Hurthle cells in fine needle aspiration biopsy for multinodular goitre. Endocr Regul. 2010;44(2):65–8. https://doi.org/10.4149/endo_2010_02_65
70 Roh MH, Jo VY, Stelow EB, Faquin WC, Zou KH, Alexander EK, et al. The predictive value of the fine-needle aspiration diagnosis "suspicious for a follicular neoplasm, hurthle cell type" in patients with hashimoto thyroiditis. Am J Clin Pathol. 2011;135(1): 139–45. https://doi.org/10.1309/AJCP0RW2WMDUAKGK
71 Yazici P, Yilmaz B, Bozkurt E, Mihmanli M, Uludag M. Malignancy risk of oncocytic changes in thyroid nodules: who should we offer surgery to? Acta Chir Belg. 2016; 116(1):30–5. https://doi.org/10.1080/00015458.2015.1136484
72 Zhang YW, Greenblatt DY, Repplinger D, Bargren A, Adler JT, Sippel RS, et al. Older age and larger tumor size predict malignancy in hürthle cell neoplasms of the thyroid. Ann Surg Oncol. 2008;15(10): 2842–6. https://doi.org/10.1245/s10434-008-0079-8
73 Sippel RS, Elaraj DM, Khanafshar E, Zarnegar R, Kebebew E, Duh QY, et al. Tumor size predicts malignant potential in Hürthle cell neoplasms of the thyroid. World J Surg. 2008;32(5):702–7. https://doi.org/10.1007/s00268-007-9416-5
74 Kim TH, Lim JA, Ahn HY, Lee EK, Min HS, Won Kim K, et al. Tumor size and age predict the risk of malignancy in Hürthle cell neoplasm of the thyroid and can therefore guide the extent of initial thyroid surgery. Thyroid. 2010;20(11):1229–34. https://doi.org/10.1089/thy.2009.0443
75 Renshaw A. Hurthle cell carcinoma is a better gold standard than Hurthle cell neoplasm for fine-needle aspiration of the thyroid: defining more consistent and specific cytologic criteria. Cancer (Cancer Cytopathol. 2002;96(5):261–6. https://doi.org/10.1002/cncr.10797
76 Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. Am J Surg Pathol. 2007;31(8): 1256–64. https://doi.org/10.1097/PAS.0b013e3180309e6a
77 Dettmer M, Schmitt A, Steinert H, Moch H, Komminoth P, Perren A. Poorly differentiated oncocytic thyroid carcinoma--diagnostic implications and outcome. Histopathology. 2012;60(7):1045–51. https://doi.org/10.1111/j.1365-2559.2012.04188.x
78 Bai S, Baloch ZW, Samulski TD, Montone KT, LiVolsi VA. Poorly differentiated oncocytic (hurthle cell) follicular carcinoma: an institutional experience. Endocr Pathol. 2015;26(2):164–9. https://doi.org/10.1007/s12022-015-9367-6
79 Nakaguro M, Faquin WC, Baloch ZW, Cantley RL, Compton ML, Ely KA, et al. Fine needle aspiration of salivary gland carcinomas with high-grade transformation: a multi-institutional study of 22 cases and review of the literature. Cancer Cytopathol. 2021;129(4):318–25. https://doi.org/10.1002/cncy.22388
80 Tondi Resta I, Gubbiotti MA, Montone KT, Livolsi VA, Baloch ZW. Differentiated high grade thyroid carcinomas: diagnostic consideration and clinical features. Hum Pathol. 2024;144:53–60. https://doi.org/10.1016/j.humpath.2024.01.002

81 Torous VF, Jitpasutham T, Baloch Z, Cantley RL, Kerr DA, Liu X, et al. Cytologic features of differentiated high-grade thyroid carcinoma: a multi-institutional study of 40 cases. Cancer Cytopathol. 2024;132(8):525–36. https://doi.org/10.1002/cncy.22874
82 Landa I, Ibrahimpasic T, Boucai L, Sinha R, Knauf JA, Shah RH, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Investig. 2016;126(3):1052–66. https://doi.org/10.1172/JCI85271
83 Canberk S, Onenerk M, Gunes P, Sayman E, Kilicoglu G. Oncocytic variant of medullary thyroid carcinoma. Endocr Pathol. 2015;26(4):320–3. https://doi.org/10.1007/s12022-015-9389-0
84 Onenerk M, Canberk S, Gunes P, Erkan M, Kilicoglu GZ. Oncocytic variant of poorly differentiated thyroid carcinoma: "Is diagnosis possible by fine-needle aspiration? CytoJournal. 2016;13:23. https://doi.org/10.4103/1742-6413.192188
85 Anwar F. The phenotype of Hurthle and Warthin-like papillary thyroid carcinomas is distinct from classic papillary carcinoma as to the expression of retinoblastoma protein and E2F-1 transcription factor. Appl Immunohistochem Mol Morphol. 2003;11(1):20–7. https://doi.org/10.1097/00129039-200303000-00004
86 Apel RL, Asa SL, LiVolsi VA. "Warthin-like tumor" of the thyroid. Am J Surg Pathol. 1995;19(7):810–4. https://doi.org/10.1097/00000478-199507000-00009
87 Asa SL. My approach to oncocytic tumours of the thyroid. J Clin Pathol. 2004;57(3):225–32. https://doi.org/10.1136/jcp.2003.008474
88 Hong JH, Yi HS, Yi S, Kim HW, Lee J, Kim KS. Implications of oncocytic change in papillary thyroid cancer. Clin Endocrinol. 2016;85(5):797–804. https://doi.org/10.1111/cen.13115
89 Apel RL, Asa SL, LiVolsi VA. "Warthin-like tumor" of the thyroid. Am J Surg Pathol. 1995;19(7):810–4. https://doi.org/10.1097/00000478-199507000-00009
90 Baloch ZW, LiVolsi VA. Warthin-like papillary carcinoma of the thyroid. Arch Pathol Lab Med. 2000;124(8):1192–5. https://doi.org/10.5858/2000-124-1192-WLPCOT
91 Ahn J, Jin M, Kim WG, Kim TY, Kim WB, Shong YK, et al. Limitations of fine-needle aspiration and core needle biopsies in the diagnosis of tall cell variant of papillary thyroid carcinoma. Clin Endocrinol. 2023;98(1):110–6. https://doi.org/10.1111/cen.14735
92 Ghossein RA, Leboeuf R, Patel KN, Rivera M, Katabi N, Carlson DL, et al. Tall cell variant of papillary thyroid carcinoma without extrathyroid extension: biologic behavior and clinical implications. Thyroid. 2007;17(7):655–61. https://doi.org/10.1089/thy.2007.0061
93 Liu Z, Zeng W, Chen T, Guo Y, Zhang C, Liu C, et al. A comparison of the clinicopathological features and prognoses of the classical and the tall cell variant of papillary thyroid cancer: a meta-analysis. Oncotarget. 2017;8(4):6222–32. https://doi.org/10.18632/oncotarget.14055
94 Berho M, Suster S. The oncocytic variant of papillary carcinoma of the thyroid: a clinicopathologic study of 15 cases. Hum Pathol. 1997;28(1):47–53. https://doi.org/10.1016/s0046-8177(97)90278-1
95 Carr AA, Yen TWF, Ortiz DI, Hunt BC, Fareau G, Massey BL, et al. Patients with oncocytic variant papillary thyroid carcinoma have a similar prognosis to matched classical papillary thyroid carcinoma controls. Thyroid. 2018;28(11):1462–7. https://doi.org/10.1089/thy.2017.0603
96 Spaulding SL, Ho R, Everest S, Chai RL. The role of molecular testing in the diagnosis of medullary thyroid cancer: a case report of oncocytic medullary thyroid carcinoma and review of the literature. Am J Otolaryngol. 2020;41(1):102312. https://doi.org/10.1016/j.amjoto.2019.102312
97 Sams SB, Tompkins KD, Mayson S, Raeburn CD, Mehrotra S. Oncocytic variant of medullary thyroid carcinoma; a rare tumor with numerous diagnostic mimics by fine needle aspiration. Diagn Cytopathol. 2017;45(12):1148–52. https://doi.org/10.1002/dc.23790
98 Parampalli Srinivas S, Das J, Monappa V. Oncocytic variant of medullary thyroid carcinoma-A case report. Iran J Pathol. 2019;14(1):83–7. https://doi.org/10.30699/IJP.14.1.83
99 Tranchida P, Estigarribia J, Sethi S, Giorgadze T. Cytologic diagnosis of recurrent medullary thyroid carcinoma with oncocytic change twenty-one years post-thyroidectomy: case report and review of the literature. Diagn Cytopathol. 2011;39(9):641–6. https://doi.org/10.1002/dc.21438
100 Sala TD, Mureşan S, Roman R, Lazăr A, Ion R, Paşcanu I. Hypercalcaemic crisis due to primary hyperparathyroidism: report of two cases. J Crit Care Med. 2019;5(1):34–9. https://doi.org/10.2478/jccm-2019-0004
101 de Koster EJ, Corver WE, de Geus-Oei LF, Oyen WJG, Ruano D, Schepers A, et al. A clinically applicable molecular classification of oncocytic cell thyroid nodules. Endocr Relat Cancer. 2023;30(9):e230047. https://doi.org/10.1530/ERC-23-0047
102 Gopal RK, Kübler K, Calvo SE, Polak P, Livitz D, Rosebrock D, et al. Widespread chromosomal losses and mitochondrial DNA alterations as genetic drivers in Hürthle cell carcinoma. Cancer Cell. 2018;34(2):242–55. e5. https://doi.org/10.1016/j.ccell.2018.06.013
103 Frank AR, Li V, Shelton SD, Kim J, Stott GM, Neckers LM, et al. Mitochondrial-encoded complex I impairment induces a targetable dependency on aerobic fermentation in hurthle cell carcinoma of the thyroid. Cancer Discov. 2023;13(8):1884–903. https://doi.org/10.1158/2159-8290.CD-22-0982
104 Corver WE, van Wezel T, Molenaar K, Schrumpf M, van den Akker B, van Eijk R, et al. Near-haploidization significantly associates with oncocytic adrenocortical, thyroid, and parathyroid tumors but not with mitochondrial DNA mutations. Genes Chromosomes Cancer. 2014;53(10):833–44. https://doi.org/10.1002/gcc.22194
105 Corver WE, Ruano D, Weijers K, den Hartog WCE, van Nieuwenhuizen MP, de Miranda N, et al. Genome haploidisation with chromosome 7 retention in oncocytic follicular thyroid carcinoma. PLoS One. 2012;7(6):e38287. https://doi.org/10.1371/journal.pone.0038287
106 Ganly I, Makarov V, Deraje S, Dong Y, Reznik E, Seshan V, et al. Integrated genomic analysis of hurthle cell cancer reveals oncogenic drivers, recurrent mitochondrial mutations, and unique chromosomal landscapes. Cancer Cell. 2018;34(2):256–70 e5. https://doi.org/10.1016/j.ccell.2018.07.002
107 Hellgren LS, Stenman A, Jatta K, Condello V, Larsson C, Zedenius J, et al. Catching the silent culprits: TERT promoter mutation screening of minimally invasive follicular and oncocytic thyroid carcinoma in clinical practice. Endocr Pathol. 2024;35(4):411–8. https://doi.org/10.1007/s12022-024-09828-x
108 Wang X, Liu Y, Chen L, Zhang J, Jiang R, Zhang L, et al. Oncocytic cell carcinoma of the thyroid with TERT promoter mutation presenting as asphyxia in an elderly: a case report. Front Endocrinol. 2024;15:1349114. https://doi.org/10.3389/fendo.2024.1349114
109 Ganly I, Ricarte Filho J, Eng S, Ghossein R, Morris LGT, Liang Y, et al. Genomic dissection of Hurthle cell carcinoma reveals a unique class of thyroid malignancy. J Clin Endocrinol Metab. 2013;98(5):E962–72. https://doi.org/10.1210/jc.2012-3539
110 Maxwell EL, Palme CE, Freeman J. Hurthle cell tumors: applying molecular markers to define a new management algorithm. Arch Otolaryngol Head Neck Surg. 2006;132(1):54–8. https://doi.org/10.1001/archotol.132.1.54
111 Raghunathan R, Longstaff XR, Hughes EG, Li SJ, Sant VR, Tseng CH, et al. Diagnostic performance of molecular testing in indeterminate (Bethesda III and IV) thyroid nodules with Hurthle cell cytology. Surgery. 2024;175(1):221–7. https://doi.org/10.1016/j.surg.2023.05.046
112 Belaiche A, Morand GB, Turkdogan S, Kang ES, Forest VI, Pusztaszeri MP, et al. Molecular markers in follicular and oncocytic thyroid carcinomas: clinical application of molecular genetic testing. Curr Oncol. 2024;31(10):5919–28. https://doi.org/10.3390/curroncol31100441

113 Nikiforov YE, Steward DL, Robinson-Smith TM, Haugen BR, Klopper JP, Zhu Z, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. J Clin Endocrinol Metab. 2009;94(6):2092–8. https://doi.org/10.1210/jc.2009-0247
114 Moses W, Weng J, Sansano I, Peng M, Khanafshar E, Ljung BM, et al. Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. World J Surg. 2010;34(11):2589–94. https://doi.org/10.1007/s00268-010-0720-0
115 Ohori NP, Nikiforova MN, Schoedel KE, LeBeau SO, Hodak SP, Seethala RR, et al. Contribution of molecular testing to thyroid fine-needle aspiration cytology of "follicular lesion of undetermined significance/atypia of undetermined significance". Cancer Cytopathol. 2010;118(1):17–23. https://doi.org/10.1002/cncy.20063
116 Giordano TJ, Beaudenon-Huibregtse S, Shinde R, Langfield L, Vinco M, Laosinchai-Wolf W, et al. Molecular testing for oncogenic gene mutations in thyroid lesions: a case-control validation study in 413 post-surgical specimens. Hum Pathol. 2014;45(7):1339–47. https://doi.org/10.1016/j.humpath.2014.03.010
117 Eszlinger M, Piana S, Moll A, Bösenberg E, Bisagni A, Ciarrocchi A, et al. Molecular testing of thyroid fine-needle aspirations improves presurgical diagnosis and supports the histologic identification of minimally invasive follicular thyroid carcinomas. Thyroid. 2015;25(4):401–9. https://doi.org/10.1089/thy.2014.0362
118 Labourier E, Shifrin A, Busseniers AE, Lupo MA, Manganelli ML, Andruss B, et al. Molecular testing for miRNA, mRNA, and DNA on fine-needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. J Clin Endocrinol Metab. 2015;100(7):2743–50. https://doi.org/10.1210/jc.2015-1158
119 Carty SE, Ohori NP, Hilko DA, McCoy KL, French EK, Manroa P, et al. The clinical utility of molecular testing in the management of thyroid follicular neoplasms (Bethesda IV nodules). Ann Surg. 2020;272(4):621–7. https://doi.org/10.1097/SLA.0000000000004130
120 Welschmeyer A, Kligerman M, Noel J. Management of indeterminate thyroid nodules: a model comparing surgery, molecular testing, and observation. Otolaryngol Head Neck Surg. 2024;171(5):1349–54. https://doi.org/10.1002/ohn.958
121 Lastra RR, Pramick MR, Crammer CJ, Li-Volsi VA, Baloch ZW. Implications of a suspicious afirma test result in thyroid fine-needle aspiration cytology: an institutional experience. Cancer Cytopathol. 2014;122(10):737–44. https://doi.org/10.1002/cncy.21455
122 Parajuli S, Jug R, Ahmadi S, Jiang XS. Hurthle cell predominance impacts results of Afirma gene expression classifier and ThyroSeq molecular panel performance in indeterminate thyroid nodules. Diagn Cytopathol. 2019;47(11):1177–83. https://doi.org/10.1002/dc.24290
123 Harrell RM, Bimston DN. Surgical utility of Afirma: effects of high cancer prevalence and oncocytic cell types in patients with indeterminate thyroid cytology. Endocr Pract. 2014;20(4):364–9. https://doi.org/10.4158/EP13330.OR
124 Sacks WL, Bose S, Zumsteg ZS, Wong R, Shiao SL, Braunstein GD, et al. Impact of Afirma gene expression classifier on cytopathology diagnosis and rate of thyroidectomy. Cancer. 2016;124(10):722–8. https://doi.org/10.1002/cncy.21749
125 Krane JF, Cibas ES, Endo M, Marqusee E, Hu MI, Nasr CE, et al. The Afirma Xpression Atlas for thyroid nodules and thyroid cancer metastases: insights to inform clinical decision-making from a fine-needle aspiration sample. Cancer Cytopathol. 2020;128(7):452–9. https://doi.org/10.1002/cncy.22300
126 Loncar I, van Velsen EFS, Massolt ET, van Kemenade FJ, van Engen-van Grunsven ACH, van Hemel BM, et al. European experience with the Afirma Gene Expression Classifier for indeterminate thyroid nodules: a clinical utility study in The Netherlands. Head Neck. 2023;45(9):2227–36. https://doi.org/10.1002/hed.27472
127 Vardarli I, Tan S, Görges R, Krämer BK, Herrmann K, Brochhausen C. Diagnostic accuracy of Afirma gene expression classifier, Afirma gene sequencing classifier, ThyroSeq v2 and ThyroSeq v3 for indeterminate (Bethesda III and IV) thyroid nodules: a meta-analysis. Endocr Connect. 2024;13(7):e240170. https://doi.org/10.1530/EC-24-0170
128 Nasr CE, Andrioli M, Endo M, Harrell RM, Livhits MJ, Osakwe I, et al. Real-world performance of the afirma genomic sequencing classifier (GSC)-A meta-analysis. J Clin Endocrinol Metab. 2023;108(6):1526–32. https://doi.org/10.1210/clinem/dgac688
129 Kandil E, Metz TA, Issa PP, Aboueisha M, Omar M, Attia AS, et al. Diagnostic performance of afirma and interpace diagnostics genetic testing in indeterminate thyroid nodules: a single center study. Cancers. 2023;15(7):2098. https://doi.org/10.3390/cancers15072098
130 Lupo MA, Walts AE, Sistrunk JW, Giordano TJ, Sadow PM, Massoll N, et al. Multiplatform molecular test performance in indeterminate thyroid nodules. Diagn Cytopathol. 2020;48(12):1254–64. https://doi.org/10.1002/dc.24564
131 Zhang M, Hu X, Liu L, Wang Y, Jiang J, Li H, et al. Clinical value of multi-gene testing in distinguishing benign and malignant thyroid nodules. Medicine. 2024;103(4):e35960. https://doi.org/10.1097/MD.0000000000035960
132 Walsh PS, Wilde JI, Tom EY, Reynolds JD, Chen DC, Chudova DI, et al. Analytical performance verification of a molecular diagnostic for cytology-indeterminate thyroid nodules. J Clin Endocrinol Metab. 2012;97(12):E2297–306. https://doi.org/10.1210/jc.2012-1923