Seminars in Diagnostic Pathology 37 (2020) 234–242

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Hürthle-cell neoplasms of the thyroid: An algorithmic approach to pathologic diagnosis in light of molecular advances

Jalal B. Jalaly, Zubair W. Baloch*

Hospital of the University of Pennsylvania, Department of Pathology, Philadelphia, (PA), United States

ARTICLE INFO

Keywords:
Hürthle cell neoplasm
Hürthle cell carcinoma
Oncocyte
Molecular advances
Algorithmic approach

ABSTRACT

Our understanding of neoplasia is evolving at a rapid pace in these exciting times, where recent molecular pathology advances are reinforcing and fine tuning morphological divisions and classification. Thyroid gland neoplasia in general, and Hürthle-cell neoplasms in particular, are no exception in the current era of histopathology-molecular biology paradigm. In this review paper, we discuss the rationale that led pathologists in the past to separate Hürthle-cell neoplasms into its own dedicated diagnostic category, and provide an algorithmic approach to the differential diagnosis of oncocytic lesions of the thyroid. This review will also shed light on the current WHO classification of Hürthle-cell neoplasms in light of molecular advances that justify histopathologic distinctions.

The Oncocyte

An "oncocyte" is an enlarged polygonal cell with an abundant granular eosinophilic cytoplasm, round nuclei with even chromatin pattern and prominent nucleoli. The term "oncocyte" was first defined by Hamprel in 1931, and a tumor arising from these cells in a parotid gland was termed "oncocytoma" in 1932 by Jaffe.[1, 2] Electron microscopy studies have shown that this peculiar cytoplasmic eosinophilia is due to the accumulation of numerous enlarged and globular mitochondria.[3–5] It has been shown that oncocytic change represents a cellular response due to mitochondrial adaptive homeostasis. Cells from different organs undergo oncocytic change including breast, salivary gland, thyroid, parathyroid, pituitary and kidney. The oncocytes are named differently in each organ. For example, they are referred to as apocrine cells in the breast and as Hürthle cells in the thyroid gland. The latter being a misnomer, since Karl Hürthle described parafollicular cells (now known as C-cells) in the thyroid gland[6]; however, it was actually Askanazy who first described oncocytic change in follicular cells of the human thyroid gland.[7] Interestingly, varying degrees of cytoplasmic eosinophilia can occur in thyroid follicular cells. It will not be farfetched to assume that this most likely represents an early adaptive cellular change eventually resulting in classic Hürthle cell morphology.

Hürthle-cell neoplasms of the thyroid gland: general pathologic concepts

The thyroid gland can show oncocytes either as few scattered cells lining follicles, cellular aggregates, or well-defined unencapsulated, partially or completely encapsulated nodules. 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.

Hürthle-cell neoplasms are rare compared to other follicular cell derived thyroid tumors. In the 2004 edition of WHO Classification of the Endocrine Organs,[8] 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.[9] As defined by WHO, Hürthle-cell neoplasms are composed of 75% or greater Hürthle cells.[9]

In the early literature, some authors considered all Hürthle-cell neoplasms of the thyroid gland as malignant, because some of the lesions classified as benign Hürthle-cell neoplasms behaved in a malignant fashion.[10–12] However, these findings were later disputed by reports based on strict application of diagnostic criteria to differentiate between benign and malignant Hürthle-cell neoplasms and meticulous clinical follow-up.[13–17]

In this review, we describe an algorithmic approach (Figs. 1 and 2)

* Corresponding author.
E-mail address: baloch@pennmedicine.upenn.edu (Z.W. Baloch).

https://doi.org/10.1053/j.semdp.2020.03.004

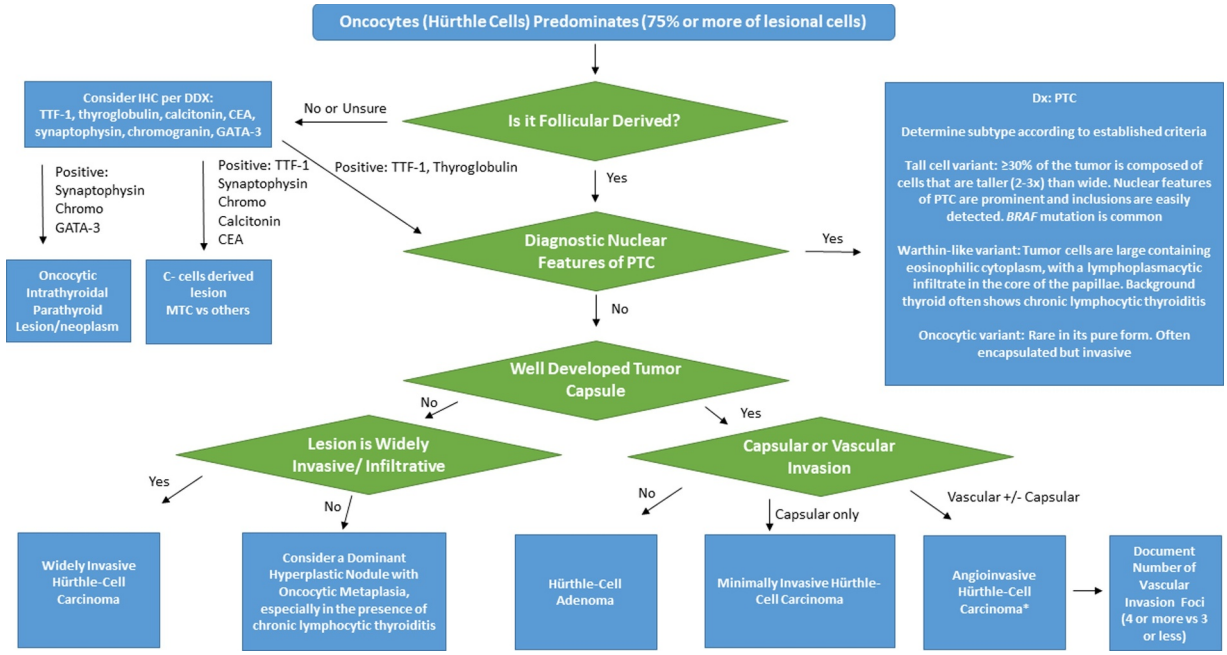

Fig. 1. An algorithmic approach to oncocytic lesions in surgical pathology.
* Some authors combine focal angioinvasion (less than 4 foci) with minimally invasive follicular carcinoma, while they consider extensive angioinvasion with widely invasive follicular carcinoma. Our personal approach is similar to the 2017 WHO with separating angioinvasive follicular or Hürthle-cell carcinoma into its own category.
Abbreviations: Chromo: chromogranin. Dx: Diagnosis. DDX: Differential diagnosis. IHC: Immunohistochemistry. MTC: Medullary thyroid carcinoma. PTC: Papillary thyroid carcinoma.

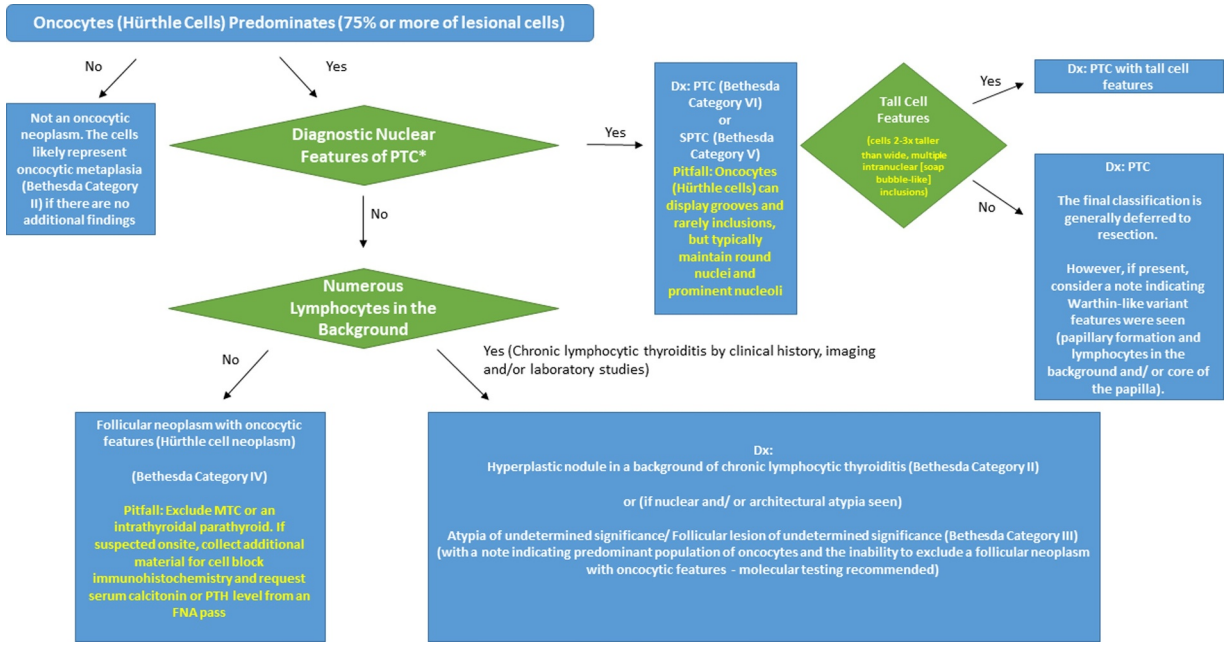

Fig 2. An algorithmic approach to oncocytic lesions in cytopathology.
* Nuclear crowding, elongation, chromatin clearing, nuclear grooves, and inclusions.
Abbreviations: Dx: Diagnosis. MTC: Medullary thyroid carcinoma. PTC: Papillary thyroid carcinoma. PTH: Parathyroid hormone. SPTC: Suspicious for papillary thyroid carcinoma.

to the pathologic diagnosis of Hürthle-cell neoplasms of the thyroid gland, in light of the recent molecular advances.

The following should be considered in diagnosing a Hürthle-cell neoplasm of the thyroid gland.

Establishing the origin of a Hürthle/oncocytic thyroid lesion

Answering this basic question is the first step to avoid pitfalls while evaluating Hürthle /oncocytic lesions of the thyroid, especially in limited tissue samples procured by fine-needle aspiration (FNA) and core biopsies. Oncocytic change can be encountered in medullary thyroid carcinoma and intrathyroidal parathyroid lesions.

Table 1
The differential diagnosis of oncocytic lesion in the thyroid.

Diagnosis	Morphological Clues and Immunohistochemistry
Medullary thyroid carcinoma	Eccentric nucleus with salt and pepper chromatin, tumor cells spindling, presence of amyloid, positive for calcitonin, CEA, TTF-1, synaptophysin, and chromogranin
Intrathyroidal parathyroid with oncocytic features	Trabecular or cord-like arrangement of cells, centrally placed small nucleus without a prominent nucleoli, presence of other cell types (chief cells or clear cells), positive for GATA-3 and PTH
Hürthle cell adenoma	Follicular growth, colloid, centrally placed large hyperchromatic nuclei with prominent nucleoli, encapsulated with no capsular or vascular invasion, positive for TTF-1, thyroglobulin, Pax-8
Hürthle cell carcinoma	Similar to Hurthle cell adenoma but with capsular or vascular invasion, widely infiltrative variants may not be encapsulated
Oncocytic variant of PTC (including tall cell and Warthin-like variants)	Nuclear features of PTC regardless of growth pattern, positive for TTF-1, Pax-8, thyroglobulin

Morphological clues that help establish follicular cell origin mainly in FNA samples is the presence of background colloid, oncocytic follicular cells partially rimmed by blebs of colloid, AKA “flame cells”, and absence of clinical, and radiological features that suggest non-follicular lesions. Clinical history of hypercalcemia (although some oncocytic parathyroid adenomas have minimal increase in serum parathyroid hormone levels) or ultrasound findings may suggest an intrathyroidal parathyroid.[18–20] In this scenario, performing PTH levels on FNA needle rinse or immunohistochemistry can establish the correct diagnosis. The presence of amyloid or spindled tumor cells may serve as clues to the possibility of an oncocytic variant of medullary thyroid carcinoma.[21–26] Fortunately, this question is easily resolved by a limited immunohistochemistry panel in ambiguous cases (Table 1).

Pathologic features

Histopathologic features

Hürthle-cell neoplasms of the thyroid are rare. The differential diagnosis includes papillary thyroid carcinoma variants demonstrating oncocytic cytoplasm, oncocytic variant of medullary thyroid carcinoma and oncocytic parathyroid lesions (see Table 1 and Figs. 3 and 4). Hürthle-cell carcinomas (HCCA) are more common in men and older patients. Most HCCAs are large tumors and demonstrate aggressive clinical behavior compared to non-Hürthle follicular carcinomas.[27–29]

On gross pathologic examination, a majority of Hürthle-cell neoplasms are partially or completely encapsulated solitary nodules, and can show a distinct mahogany brown cut surface and a central scar similar to oncocytic lesions of other organs. Most HCCAs measure greater than 3.0 cm; however, smaller tumors have been reported.[30] Intratumoral hemorrhage and partial or complete tumor infarction due to a preoperative FNA are commonly encountered in these tumors.[31]

On light microscopy, Hürthle-cell neoplasms can display varying growth patterns, the most common being solid and trabecular. However, Hürthle-cell neoplasms can also demonstrate micro and macrofollicular, pseudopapillary and rarely true papillary growth patterns. Concentric calcifications of the luminal colloid resembling psammoma bodies can be seen in Hürthle-cell neoplasms.[16,17,28,32,33] Furthermore, nuclear grooves and rarely poorly formed intranuclear pseudo-inclusions can also be seen in Hürthle cells, especially in cytology preparations.[34] These features may pose diagnostic challenges in differentiating a Hürthle-cell neoplasm from papillary thyroid carcinoma (see also the differential diagnosis section). Clear-cell change is

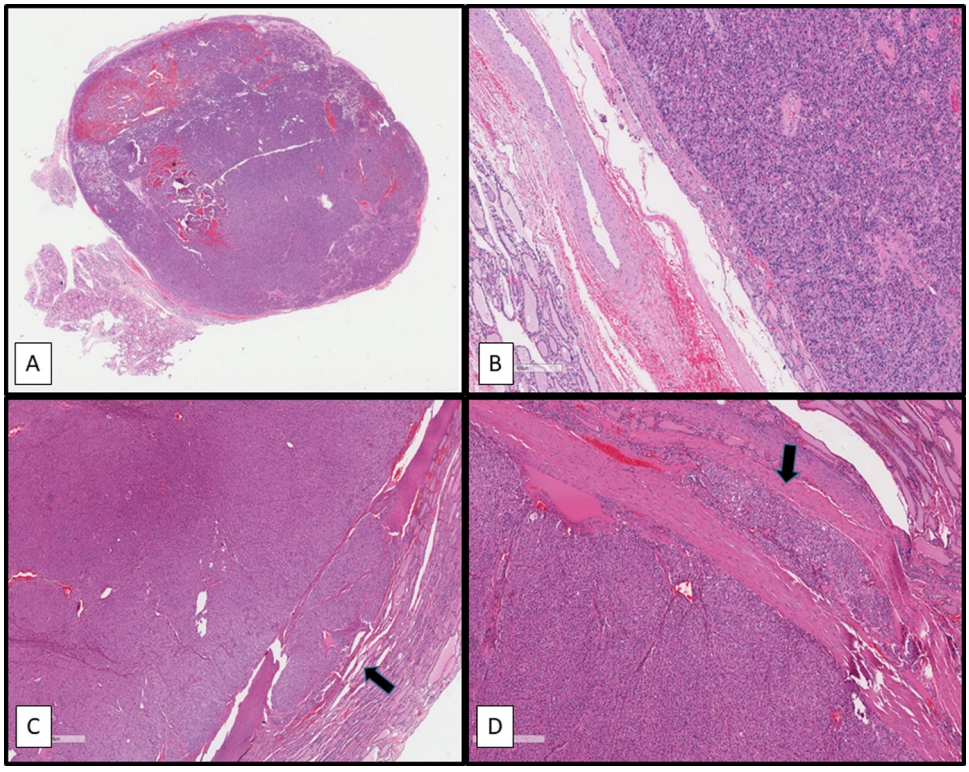

Fig. 3. Hürthle-cell adenoma (A and B) and carcinoma (C and D). Black arrows indicate foci of capsular (C) and vascular (D) invasion.

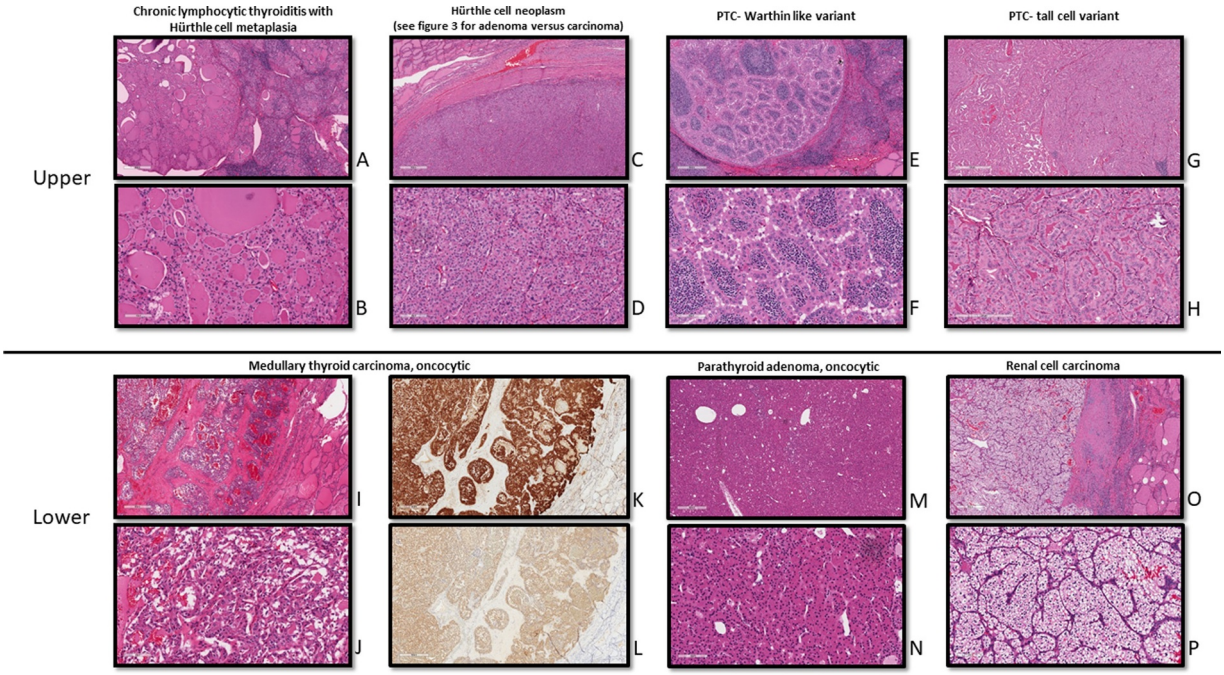

Fig. 4. Oncocytic lesions in the thyroid gland. Upper panel: follicular derived lesions. Lower panel: Non-follicular derived lesions. Chronic lymphocytic thyroiditis with Hürthle-cell metaplasia, 400x (A) and 2000x (B). Hürthle-cell neoplasm, 400x (C) and 2000x (D). Papillary thyroid carcinoma, Warthin-Like Variant, 400x (E) and 2000x (F). Papillary thyroid carcinoma, tall cell variant, 400x (G) and 2000x (H). Medullary thyroid carcinoma, 400x (I), 2000x (J), CEA (K) and calcitonin (L). Oncocytic parathyroid, 400x (M) and 2000x (N). Metastatic clear renal cell carcinoma, 400x (O) and 2000x (P).
Abbreviations: PTC: Papillary thyroid carcinoma.

not uncommon in Hürthle-cell neoplasms; however, metastasis from a clear cell carcinoma should be entertained if the tumor mostly consists of clear cells (Fig. 4O and 4P).[33]

The presence or absence of invasive characteristics in an encapsulated Hürthle-cell neoplasm (i.e. invasion into the tumor capsule and/or capsular vessels [angioinvasion]) distinguishes Hürthle-cell adenoma from carcinoma (Fig. 3). Tumor size, nuclear atypia, cellular pleomorphism and mitoses in a Hürthle-cell neoplasm are not independent predictors of malignancy. Similar to follicular thyroid carcinoma, HCCA is classified to minimally invasive, encapsulated angioinvasive and widely invasive.[9] The minimally invasive terminology is restricted for tumors showing only tumor capsule invasion, whereas the encapsulated angioinvasive tumors are further subdivided into tumors showing limited (less than four vessels) or extensive (equal to or greater than four vessels) vascular invasion.[9, 35]

The diagnosis of HCCA as well as non-Hürthle cell follicular carcinoma based solely on tumor capsule invasion is controversial, as none of these cases (which have been adequately sampled) have shown malignant behavior on clinical follow-up. This controversy is further inflamed by what constitutes capsular invasion; whether it is invasion into the tumor capsule only or one which invades into and through the tumor capsule.[36] In our practice, we do classify adequately sampled (sampling of the entire capsule and tumor interface) Hürthle-cell neoplasms as minimally invasive showing either invasion into or through the entire width of the tumor capsule.[37–41]

All pathologists agree that a Hürthle-cell neoplasm associated with invasion either into the vessels within the tumor capsule or beyond is a HCCA. It has been shown that vascular invasion is an important risk factor for tumor recurrence and distant metastasis. Specifically, higher risk of tumor recurrence is noted in cases involving four or more vessels.[35] The criteria for vascular invasion include an endothelial lined tumor thrombus attached to a vessel wall. However, the pathologic criteria for vascular invasion should be applied strictly to avoid overdiagnosis. Because Hürthle-cell neoplasms are richly vascularized and stroma-poor, manipulation during surgery and gross pathologic examination can lead to displacement of the tumor cells within capsular vessels mimicking angioinvasion.[36]

It is well-known that post FNA changes (AKA Worrisome Histologic Alteration Following Fine-Needle Aspiration – WHAFFT) are more common in Hürthle-cell neoplasms compared to other thyroid lesions[31,42] These can range from reactive nuclear atypia, inflammation and vascular proliferation around the needle track to necrosis and infarction. In rare instances, it may be difficult to differentiate between Hürthle-cell adenoma and carcinoma in cases with near total or complete infarction. It has been recommended to diagnose these as "Hürthle-cell neoplasm with extensive infarction without definite evidence of invasive features" with a comment explaining the difficulties in definite pathologic characterization.[28]

The widely invasive HCCA does not pose any diagnostic challenges as it is associated with extensive invasion into the tumor capsule, involvement of surrounding thyroid and angioinvasion.[9]

The dedifferentiation of HCCA to poorly differentiated and anaplastic carcinoma has been reported.[43–48] The poorly differentiated oncocytic carcinomas usually present as large tumors with insular/trabecular/solid growth patterns, marked nuclear pleomorphism, mitoses and foci of confluent necrosis. Some cases may also show a small cell component. These tumors show readily identifiable foci of capsular and vascular invasion.[28,33,49]

Cytopathologic features

In FNA specimens one can readily recognize the spectrum of oncocytic change. At one end of the spectrum are the follicular cells with small to medium round nuclei without prominent nucleoli and without sharp cytoplasmic outlines, and on the other are the so called Hürthle cells as classic polygonal cells with abundant and granular cytoplasm, sharp cytoplasmic borders and housing an enlarged round nucleus with prominent nucleolus.[34,50] On Diff-Quik (Romanowsky type) stain, the cytoplasm appears purple and the cytoplasmic granules are easier to identify (Fig. 5A). On Papanicolaou-stained smears, the nuclear chromatin is coarse and the prominent nucleoli is striking (Fig. 5B).

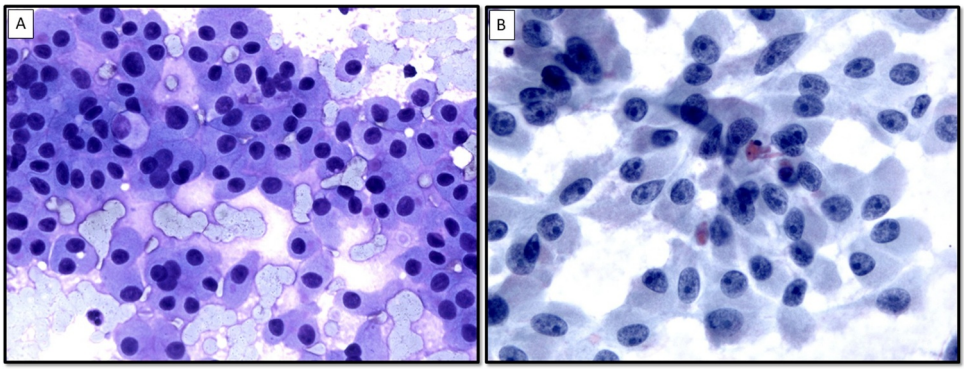

Fig. 5. Hürthle cells in cytology Diff-Quik (A) and Pap stains (B).

As aforementioned, oncocytic follicular cells can be seen in aspirates of adenomatoid nodules in the setting of euthyroid goiter, chronic lymphocytic thyroiditis and toxic nodular goiter. An aspirate containing >75% of oncocytic follicular cells or Hürthle cells should be classified as "suspicious for or consistent with follicular neoplasm with oncocytic features (Bethesda Category IV)". The majority of FNA specimens from Hürthle cell neoplasms (adenoma or carcinoma) are hypercellular and contain Hürthle cells in cohesive groups, monolayer sheets and three dimensional structures. Follicle formation can also be seen in aspirates of Hürthle-cell neoplasms.[34] In most cases, background colloid is either scant or absent; however, watery colloid has been reported in aspirates of HCCA, especially those containing macrofollicles.[51]

Random nuclear atypia in the form of nuclear enlargement, multinucleation, cellular pleomorphism and prominent nucleoli can be encountered in aspirates of Hürthle-cell neoplasms.[52] Presence of intracytoplasmic holes/lumina and transgressing vessels among cell groups have also been reported in FNA specimens of Hürthle-cell neoplasms compared to non-neoplastic proliferations.[53,54]

Differential diagnosis

As noted above, the differential diagnosis of an oncocytic thyroid neoplasm includes papillary thyroid carcinoma variants with oncocytic features, oncocytic variant of medullary thyroid carcinoma, oncocytic lesions of the parathyroid gland and metastatic tumors.

Papillary thyroid carcinoma (PTC) is unique among other malignancies because its diagnosis is based on well characterized nuclear features. The importance of these nuclear features was identified early in the surgical pathology literature.[55,56] They include nuclear enlargement and crowding, chromatin clearing, nuclear membrane irregularities, nuclear grooves and pseudoinclusions. The three main papillary thyroid carcinoma variants with abundant eosinophilic cytoplasm are: Tall cell variant (TCV), Warthin-like variant, and oncocytic variant. PTC-TCV tumor cells are at least 2-3 times longer than wide, and therefore appear columnar. The nuclear features in this variant are well-developed and pose no diagnostic problems. The Warthin-like variant shows a prominent lymphocytic infiltrate involving the tumor papillary fronds, resembling Warthin tumor in salivary glands. The oncocytic variant is the least common, especially in its pure form, and most controversial. It shows complex branching papillae and contains greater than 75% oncocytic tumor cells with nuclear features of PTC. A recent study compared the oncocytic variant of PTC with classic PTC.[57] The oncocytic variant of PTC occurs in older patients and the tumor size is larger. However, recurrence and disease specific survival did not differ between the two, which is supported by others as well.[58,59]

Oncocytic Variant of Medullary Thyroid Carcinoma is rare; and shows nested or trabecular growth pattern with interspersed intratumoral hyaline stroma. The tumor cells demonstrate characteristic neuroendocrine nuclear chromatin. The diagnosis of medullary carcinoma can be confirmed by immunoreactivity for TTF-1, calcitonin, synaptophysin, chromogranin, and CEA, but not for thyroglobulin or pax-8 (Fig. 1).[21–26]

Parathyroid glands can show few poorly circumscribed collections of oncocytic cells. Oncocytic parathyroid adenomas are rare (Fig. 4M and 4N). It may be difficult to differentiate between oncocytic parathyroid neoplasms and Hürthle-cell neoplasms, especially in FNA samples. Ancillary studies such as PTH analysis of the FNA aspirate and/or immunostains are helpful in arriving at a correct diagnosis. A limited number of oncocytic parathyroid carcinomas have been reported in the literature.[18,19,60,61]

Clinical behavior

There is much debate in the literature regarding the clinical behavior, prognosis and optimal treatment of HCCA.[27, 62, 63] Some studies have reported that the biologic behavior of HCCA is considerably different from non-Hürthle follicular carcinoma; the former with more frequent lymph nodes and distant metastasis. Others conclude that the prognosis of HCCA is similar to non-Hürthle counterparts when disease stage is taken into account.[14–16,27,45,63,64] While HCCA may lose their ability to uptake radioactive iodine, total thyroidectomy followed by radioactive iodine still remain the standard of care for most patients.[29,63,65]

Molecular characterization of Hürthle-cell carcinoma

The morphological distinction of Hürthle-cell carcinoma from the non- Hürthle follicular carcinoma is supported by the unique molecular profiles of both malignant neoplasms.[66–69] Follicular carcinoma frequently shows RAS (K-RAS, H-RAS, N-RAS) mutations. However, these mutations are rather infrequent (10–15%) in HCCA. *BRAF* V600E mutation is almost non-existent in HCCA, in contrast to PTC. The molecular profile of HCCA has been studied extensively.[60,68–83] The molecular changes of HCCA can be divided into the following (Table 2):

Abnormal number of chromosomes

Corver et al were among the first to describe the near haploid genome unique to HCCA.[71] None of the papillary and non-Hürthle follicular thyroid carcinomas studied displayed this unique karyotype. Interestingly, chromosome 7 maintained a heterozygous status in the analyzed cohort of neoplasms. These unique findings were also supported by subsequent studies.[60,75, 78] More recently, two large studies by Ganly et al and Gopal et al evaluated 56 and 70 cases of HCCA, respectively. Both studies identified the unique near-haploid genome of HCCA. Chromosome 7 also gained additional copies in many HCCAs. These additional copies were due to genome wide duplication that lead to loss of heterozygosity in the haploid chromosomes. The *BRAF* gene is housed on chromosome 7, and the additional copies provide alternative methods of gene amplification/ overexpression. Other chromosomes that frequently maintained heterozygous status with or without

Table 2
The molecular profile of Hürthle cell carcinoma (Follicular Thyroid Carcinoma, Oncocytic Variant).

Study (No. of cases)	Method	Findings
Tuin K et 2019[35]	DNA variant analysis, Sanger sequencing	***Other*s** *TERT* (24%), *RAS* (3%), *ETV6-NTRK3* (3%)
Gopal RK 2018[70]	Whole exome sequencing	***Chromosomal aberrations*** Near haploid genome (54%) Genome wide duplication (20%) Loss of heterozygosity (LOH) with heterozygous chromosomes 5, 7, 12, and 20
	FISH analysis	***Mitochondrial DNA*** Mutations in genes coding complex I (60%) *ND5* (20%), *ND2* (15%), *ND4* (15%), *ND1* (13%), *ND3* (3%), *ND4L* (3%), *ND6* (3%) Others: *CO1* (5%), *CO2* (5%), *CYB* (3%) MtDNA common deletion not detected
	Imaging flow cytometry	***Other*s** *TERT* (32%), *DAXX* (17%), *NF1* (17%), *TP53* (12%), *ATM* (10%), *NRAS* (7%), *CDKN1A* (7%), *KMT2D* (7%), *ARHGAP35* (5%), *BRAF* (5%), *TSHR* (2%), *EIF1AX* (2%), *MEN1 (2%), PTEN* (5%), *MTOR* (2%), *MSH6* (2%), *NFE2L2* (2%), *HERC2* (2%), *ARHGEF3* (2%), *FBXO31* (2%), *CSF2RA* (2%), *DMD* (2%), *KDM6A* (2%), *NFE2L2* (2%), *CACNA1C* (2%), *KRAS* (2%) *PAX8-PPARγ* fusion (2%)
Ganly I 2018[56]	Whole exome sequencing	***Chromosomal aberrations*** Near haploid genome with or without genome wide duplication and loss of heterozygosity Chromosome 5, 7, 12 duplication
	RNA sequencing	***Mitochondrial DNA (71%)*** *ND1, ND2, ND4, ND4L, ND5, CYB, TL1, CO1, CO2, CO3, and ATP6* Almost all mtDNA encoding genes were involved except *ND6* and *ATP8*
	FISH analysis	***Other*s** Overall, 4,293 somatic mutations. Commonly mutated genes include: *TERT* (22%), *MADCAM1* (20%), *EIF1AX* (11%), *ERBB2* (11%), *UBXN11* (9%), *NRAS* (9%), *HLA-A* (9%), *NF1* (9%), *ALKBH7* (7%), *FAT1* (7%), *SIRPA* (7%), *NBPF1* (7%), *TP53* (7%), *ATM* (5%), *PTEN* (4%), *RET* (4%), *MET* (4%), *KRAS* (4%), *HRAS* (2%) *PIK3CA* (2%) Other commonly mutated genes include: *OR4L1, ATXN1, FAM171B, POMZP3, HRCT1, DLX6, and FRG2B* No *BRAF* mutations Recurrent in-frame coding rearrangements: *CHCHD10_VPREB3, HEPHL1_PANX1, TMEM233_PRKAB1, ACSS1_APMAP, RSPH6A_DMWD, DUOXA1_DUOX2, OSGIN1_NECAB2, BCAP29_SLC26A4, TFG_GPR128* Gene expression profiling shows significant difference between widely invasive Hürthle cell carcinoma and minimally invasive Hürthle cell carcinoma
Chindris et al 2015[61]	Targeted *TERT* sequencing	***Others*** *TERT* (13%)
Evangelisti C et al 2015[14]	Targeted *TP53, BRAF, RAS,* and nuclear genes coding mitochondrial complex I subunits sequencing RT-PCR for *RET-PTC3* *FISH for PAX8-PPARγ*	***Mitochondrial DNA*** *ND1* (21%), *ND2 (7%), ND4 (14%), ND5 (7%), CYB* (7%) ***Nuclear genes coding mitochondrial complex I subunits*** *NDUFA12, NDUFB6* ***Others*** *TP53 (14%), NRAS* (7%), *PAX8-PPARγ* (7%), No *RET-PTC*
Kasaian K 2015[74]	Whole genome sequencing and sanger sequencing of *MEN1* in two cases	***Chromosomal aberrations*** Loss of chromosomes 1, 2, 3, 4, 6, 8, 9, 11, 14, 15, 16, 21, and X (ie: near haploid genome) Extra copies in remaining chromosomes
	Targeted *MEN1* sequencing	***Others*** *MEN1 (4.2%), EWSR1, MSH2, BRCA1*
Qasem E et al 2015[3]	Targeted *TERT* and *BRAF* sequencing	***Others*** *TERT* (30%) No *BRAF* V600E mutation
Wei S 2015[9]	Massive parallel sequencing of 47 genes	***Others*** *TP53* (44%), *PTEN* (22%)
Corver WE 2014[7]	Genome wide SNP array	***Chromosomal aberrations*** Near haploid genome (43%) with or without genome wide duplication Heterozygous chromosomes 5, 7, and 12
	Flow cytometry	***Mitochondrial DNA*** *ND1* (14%), *ND3* (14%), *CO1* (14%)
	MtDNA sequencing	***Others*** No *BRAF, HRAS, NRAS, or IDH1 or IDH2* mutations
Ganly I 2013[19]	Mass spectrometry-based genotyping assays of common genes RT-PCR of common fusions comparative genomic hybridization Gene expression profiling	***Chromosomal aberrations*** Chromosomes 5,7,10,12,17 and 20 gains Chromosomal losses: 4p16, 5p15-5q35, 6p25, 7p15-7q36, 8p21-23, 10p13, 12p13-q24, 16q23, 17p13-q25 Chromosomal gains: 4q24, 6p23, 6q26, 7p15, 9q33, 13q14, 22 ***Others*** *RAS* (16%) No *RET, BRAF, PIK3CA* mutations No *RET, PPARG* rearrangement No *PIK3CA* amplifications Gene expression profiling shows significant difference between widely invasive Hürthle cell carcinoma and minimally invasive Hürthle cell carcinoma or Hürthle cell adenoma

(*continued on next page*)

Table 2 (*continued*)

Study (No. of cases)	Method	Findings
Landa I 2013[25]	Targeted *TERT* sequencing	***Others***
		TERT (16%)
Corver WE 2012[10]	Flow cytometry	***Chromosomal aberrations***
	FISH	Near-haploid with or without genome wide duplication and subsequent loss of heterozygosity
	SNP array and LAIR analysis	Heterozygous chromosome 7
		Others
		PIK3CA (c.86276A.G, p.H1047R) (10%)
De Vries MM 2012[17]	FISH analysis for *RET-PTC* and *PAX8-PPARγ*	***Others***
	Targeted *BRAF, HRAS*, and *NRAS* sequencing	*RET-PTC* (38%)
		PAX8-PPARγ (27%)
		NRAS (6%)
		No *BRAF* or *HRAS* mutations
Gasparre G 2007[22]	mtDNA sequencing	***Mitochondrial DNA***
		ND1, ND2, ND4, ND5, ATP6
Máximo V 2005[11]	Targeted GRIM-19 Sequencing	***Mitochondrial DNA***
		GRIM-19 (9%)
	LOH analysis in 19p13.2 region	***Others***
		No *BRAF* mutation or *RET/PTC* rearrangement
Máximo V 2002[13]	mtDNA sequencing	***Mitochondrial DNA***
		ND1, ND3, ND5, ND6, ATP6, CYB, CO1, CO2, CO3
		MtDNA common deletion (100% cases)
		MtDNA D-loop somatic point mutations (53.9%)

additional copies were chromosomes 5 and 12.

Corver et al. have recently showed that this near haploid genome may be due to reactive oxygen species secondary to mitochondrial DNA mutations involving complexes of the respiratory chain.[84] The mitochondrial DNA mutations lead to glycolysis dependent glucose metabolism with accumulation of reactive oxygen species. Interestingly, the near haploid genome and mitochondrial DNA mutations were shown to be early events (truncal events) in the evolution of HCCA, shared between the primary tumor, recurrence, and metastasis.[77]

Mutations targeting the mitochondrial DNA

Most mitochondrial DNA mutations involve genes encoding Complex I of the mitochondrial respiratory chain, which is composed of seven hydrophobic complex I subunits encoded by mitochondrial DNA genes (*ND1-ND6* and *ND4L*). All were shown to be mutated in HCCA, albeit with varying frequencies.[60,68,69,74,76,77] Gopal et al have shown that *ND5* is the most frequently involved, followed by *ND2, ND4*, and *ND1*. Other mitochondrial genes were mutated as well, including *CO1, CO2, CO3, CYB,* and *ATP6* being consistently mutated across different studies.[60,68,74, 76,77] Mitochondrial DNA mutations are not unique to Hürthle-cell neoplasms, as studies have shown that papillary thyroid carcinoma, non-Hürthle follicular carcinoma, and other malignancies can show these mutations.[60,68,76] The common deletion in mitochondrial DNA, which deletes between nucleotides 8,470 and 13,447 of the human mtDNA, was initially thought to be more prevalent in Hürthle-cell neoplasms[68]; however, recent studies have not corroborated these findings.[60,77]

Mutations in specific nuclear DNA genes

Among the different genes mutated in HCCA, the *TERT* promoter is frequently mutated (range 13-32%).[70,74,77,79–81] It should be noted that *TERT* promoter mutation is also described in other aggressive thyroid malignancies and is not unique to HCCA. Interestingly, minimally invasive HCCAs are less likely to show *TERT* promoter mutation compared to widely invasive/ angioinvasive HCCAs.[70,74] Some authors classify Hürthle-cell carcinomas into minimally invasive (including those with focal (<4 foci) of angioinvasion) and widely invasive (including those with ≥4 foci of angioinvasion). In that classification, minimally invasive Hürthle-cell carcinomas with *TERT* mutations also show focal angioinvasion.[70,74] It is our practice to separate angioinvasive Hürthle-cell carcinomas into its own category in line with the WHO 2017 recommendation (Fig. 1). HCCA can also display mutations in other genes involved in telomere length (*DAXX* and *ATRX*).[77]

Ganly et al showed that genes mutated in HCCA were clustered in signal transduction and tumor suppresser pathways.[74] The MAP kinase and mTOR pathways were involved in 55% of HCCA. These genes included *EIF1AX, NF1, PTEN, TSC1/2, EIF, RAS, EGFR, ERBB2, PDGFR, TSHR, MET,* and *RET*. DNA damage and repair pathway genes were mutated in 38% of tumors, namely, *ATM, TP53, CHEK2, CDKN1A, TLK1, E2F1, PML, RB1, XPC, ERCC%, BRCA1, XRCC3, MSH2, MSH3, PMS, POLE, FANCB, and FANCD2*. Epigenetic modification mutations were also seen in 59% of tumors, such as *SWI/SNF, ISWI/CHD, ARID1A, CREBBP, BRD7, KMT2C, NSD1, EZH1, HCAT7, SIRT6, PHF2, DNMT1*, among others. Mutations also occurred in ephrin genes regulating angiogenesis (16%), including *EPHA1, EPHA2, EPHA6, EPHA7, EPHA10, EPHA8, EPHB2,* and *EPHB4*.

Summary

- Hürthle-cell neoplasms are divided into Hürthle-cell adenoma and Hürthle-cell carcinoma. The latter is further divided into encapsulated minimally invasive, angioinvasive, and widely invasive Hürthle-cell carcinoma.
- Establishing follicular origin of oncocytic lesions in the thyroid is important to avoid diagnostic pitfalls in diagnosing medullary thyroid carcinoma, intrathyroidal parathyroid lesion(s), and secondary tumors of the thyroid gland.
- Papillary thyroid carcinoma variants can exhibit oncocytic cytoplasm such as tall cell, Warthin-like, and oncocytic variants.
- Near genome haplodization is unique to Hürthle-cell neoplasms and maybe secondary to mitochondrial mutations.
- *TERT* promotor mutations are more frequent in aggressive (angioinvasive and widely invasive) Hürthle-cell carcinoma.

References

1. Musholt TJ, Clerici T, Dralle H, Frilling A, Goretzki PE, Hermann MM, et al. German association of endocrine surgeons practice guidelines for the surgical treatment of benign thyroid disease. *Langenbecks Arch Surg.* 2011;396(5):639–649.
2. Tiran B, Wawschinek O, Karpf E, Hermann M, Langsteger W, Petek W, et al. [Trace element studies of thyroid tissue in a resected specimen]. *Acta Med Austriaca.* 1990;17(Suppl 1):88–89.
3. Matias C, Nunes JM, Sobrinho LG, Soares J. Giant mitochondria and intramitochondrial inclusions in benign thyroid lesions. *Ultrastructural pathol.* 1991;15(3):221–229.
4. Nesland JM, Sobrinho-simões MA, Holm R, Sambade MC, Johannessen JV. Hürthle-cell lesions of the thyroid: a combined study using transmission electron microscopy,

scanning electron microscopy, and immunocytochemistry. *Ultrastructural Pathol.* 1985;8(4):269–290.
5. Satoh M, Yagawa K. Electron microscopic study on mitochondria in Hürthle cell adenoma of thyroid. *Pathol Int.* 1981;31(6):1079–1087.
6. Hürthle K. Beiträge zur Kenntniss des Secretionsvorgangs in der Schilddrüse. *Pflügers Arch Eur J Physiol.* 1894;56(1):1–44.
7. Askanazy M. Pathologisch-anatomische Beiträge zur Kenntniss des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung. *Dtsch Arch klin Med.* 1898;61:118–186.
8. DeLellis RA, Lloyd RD, Heitz PU, Eng C, eds. *WHO: Pathology and Genetics. Tumours of Endocrine Organs.* Lyon, France: IARC Press; 2004.
9. Lloyd LR, Osamura RY, Kloppel G, Rosai J, eds. *WHO Classification of Tumours of Endocrine Organs.* 4th ed. Lyon, France: WHO/IARC Press; 2017.
10. Gundry SR, Burney RE, Thompson NW, Lloyd R. Total thyroidectomy for Hurthle cell neoplasm of the thyroid. *Arch Surg.* 1983;118(5):529–532.
11. McLeod MK, Thompson NW. Hurthle cell neoplasms of the thyroid. *Otolaryngol Clin North Am.* 1990;23(3):441–452.
12. Thompson NW, Dunn EL, Batsakis JG, Nishiyama RH. Hurthle cell lesions of the thyroid gland. *Surg Gynecol Obstet.* 1974;139(4):555–560.
13. 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):2616–2625.
14. Stojadinovic A, Hoos A, Ghossein RA, Urist MJ, Leung DH, Spiro RH, et al. Hurthle cell carcinoma: a 60-year experience. *Ann Surg Oncol.* 2002;9(2):197–203.
15. 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):582–586.
16. Tallini G. Oncocytic tumours. *Virchows Arch.* 1998;433(1):5–12.
17. Tallini G, Carcangiu ML, Rosai J. Oncocytic neoplasms of the thyroid gland. *Acta Pathol Jpn.* 1992;42(5):305–315.
18. Giorgadze T, Stratton B, Baloch ZW, LiVolsi VA. Oncocytic parathyroid adenoma: problem in cytological diagnosis. *Diagnost. Cytopathol.* 2004;31(4):276–280.
19. Paker I, Yilmazer D, Yandakci K, Arikok AT, Alper M. Intrathyroidal oncocytic parathyroid adenoma: a diagnostic pitfall on fine-needle aspiration. *Diagnost Cytopathol.* 2010;38(11):833–836.
20. Sriphrapradang C, Sornmayura P, Chanplakorn N, Trachoo O, Sae-Chew P, Aroonroch R. Fine-needle aspiration cytology of parathyroid carcinoma mimic Hürthle cell thyroid neoplasm. *Case Rep Endocrinol.* 2014;2014.
21. Canberk S, Onenerk M, Gunes P, Sayman E, Kilicoglu G. Oncocytic variant of medullary thyroid carcinoma. *Endocrine Pathol.* 2015;26(4):320–323.
22. Dedivitis RA, Di Giovanni JH, da Silva GF, Marinho LC, Guimarães AV. Oncocytic variant of medullary thyroid carcinoma: case report. *Arquivos Brasileiros de Endocrinol Metabol.* 2004;48(2):315–317.
23. Dominguez-Malagon H, Delgado-Chavez R, Torres-Najera M, Gould E, Albores-Saavedra J. Oxyphil and squamous variants of medullary thyroid carcinoma. *Cancer.* 1989;63(6):1183–1188.
24. 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. *Diagnost Cytopathol.* 2017;45(12):1148–1152.
25. Srinivas SP, Das J, Monappa V. Oncocytic variant of medullary thyroid carcinoma-a case report. *Iran J Pathol.* 2019;14(1):83.
26. Vinciguerra GLR, Noccioli N, Cippitelli C, Minucci A, Capoluongo E, Bartolazzi A. Oncocytic variant of medullary thyroid carcinoma: a rare case of sporadic multifocal and bilateral RET wild-type neoplasm with revision of the literature. *Rare tumors.* 2016;8(4):166–168.
27. 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):30–35.
28. 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 Medicine.* 2008;132(8):1241–1250.
29. Goffredo P, Roman SA, Sosa JA. Hurthle cell carcinoma: a population-level analysis of 3311 patients. *Cancer.* 2013;119(3):504–511.
30. Samulski TD, Bai S, LiVolsi VA, Montone K, Baloch Z. Malignant potential of small oncocytic follicular carcinoma/Hurthle cell carcinoma: an institutional experience. *Histopathology.* 2013;63(4):568–573.
31. Baloch ZW, LiVolsi VA. Post fine-needle aspiration histologic alterations of thyroid revisited. *Am J Clin Pathol.* 1999;112(3):311–316.
32. Asa S. My approach to oncocytic tumours of the thyroid. *J Clin Pathol.* 2004;57(3):225–232.
33. 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.
34. Kini SR. *Thyroid Cytopathology An Atlas and Text.* Ist. ed Philadelphia, PA: Lippincott Williams & Wilkins; 2008 ed.
35. Ghossein RA, Hiltzik DH, Carlson DL, Patel S, Shaha A, Shah JP, et al. Prognostic factors of recurrence in encapsulated Hurthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer: Interdiscip Int J Am Cancer Soc.* 2006;106(8):1669–1676.
36. Baloch ZW, LiVolsi VA. Pathology of follicular cancer. *Thyroid Cancer.* 2016:781–786.
37. Schmid KW, Totsch M, Ofner D, Bocker W, Ladurner D. Minimally invasive follicular thyroid carcinoma: a clinico-pathological study. *Curr Top Pathol.* 1997;91:37–43.
38. Thompson LD, Wieneke JA, Paal E, Frommelt RA, Adair CF, Heffess CS. A clinicopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. *Cancer.* 2001;91(3):505–524.
39. Yamashina M. Follicular neoplasms of the thyroid. Total circumferential evaluation of the fibrous capsule. *Am J Surg Pathol.* 1992;16(4):392–400.
40. Evans HL. Follicular neoplasms of the thyroid. A study of 44 cases followed for a minimum of 10 years with emphasis on differential diagnosis. *Cancer.* 1984;54:535–540.
41. Kahn NF, Perzin KH. Follicular carcinoma of the thyroid: an evaluation of the histologic criteria used for diagnosis. *Pathol Ann.* 1983;18(Pt 1):221–253.
42. LiVolsi VA, Merino MJ. Worrisome histologic alterations following fine-needle aspiration of the thyroid (WHAFFT). *Pathol Annu.* 1994;29((Pt 2):99–120.
43. Mai DD, Mai KT, Shamji FM. Fine needle aspiration biopsy of anaplastic thyroid carcinoma developing from a Hurthle cell tumor: a case report. *Acta Cytol.* 2001;45(5):761–764.
44. Okon K, Wierzchowski W, Jablonska E, Wojcik P, Steczko A. Anaplastic, sarcomatoid carcinoma of the thyroid originating from a Hurthle cell tumor. *Pol J Pathol.* 2003;54(4):277–281.
45. Stucchi CM, Vaccaro V, Magherini A, Di Gregorio C, Greco G, Livolsi VA, et al. Hurthle cell follicular carcinoma of the thyroid gland presenting with diffuse meningeal carcinomatosis and evolving to anaplastic carcinoma. *J Clin Pathol.* 2007;60(7):831–832.
46. Asioli S, Righi A, Volante M, Chiusa L, Lloyd RV, Bussolati G. Cell size as a prognostic factor in oncocytic poorly differentiated carcinomas of the thyroid. *Hum Pathol.* 2014;45(7):1489–1495.
47. 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):1045–1051.
48. 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.
49. 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):164–169.
50. Auger M. Hurthle cells in fine-needle aspirates of the thyroid: a review of their diagnostic criteria and significance. *Cancer Cytopathol.* 2014;122(4):241–249.
51. 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):185–193.
52. 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.
53. Elliott DD, Pitman MB, Bloom L, Faquin WC. Fine-needle aspiration biopsy of Hurthle cell lesions of the thyroid gland: A cytomorphologic study of 139 cases with statistical analysis. *Cancer.* 2006;108(2):102–109.
54. 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):1031–1035.
55. Hapke MR, Dehner LP. The optically clear nucleus. A reliable sign of papillary carcinoma of the thyroid? *Am J Surg Pathol.* 1979;3(1):31–38.
56. HIRABAYASHI RN, LINDSAY S. Carcinoma of the thyroid gland: a statistical study of 390 patients. *J Clin Endocrinol Metabol.* 1961;21(12):1596–1610.
57. Wenter V, Jellinek A, Unterrainer M, Ahmaddy F, Lehner S, Albert NL, et al. Long-term outcome of rare oncocytic papillary (Hürthle cell) thyroid carcinoma following (adjuvant) initial radioiodine therapy. *Eur J Nucl Med Mol Imag.* 2019;46(12):2526–2535.
58. 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):1462–1467.
59. Liu C, Zhao Q, Zeng W, Chen C, Ming J, Wang S, et al. Do patients with oxyphilic cell papillary thyroid carcinoma have a poor prognosis? Analysis of the surveillance, epidemiology, and end results database 2004–2013 with propensity score matching. *Oncotarget.* 2017;8(44):77075.
60. 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):833–844.
61. Maximo V, Rios E, Sobrinho-Simoes M. Oncocytic lesions of the thyroid, kidney, salivary glands, adrenal cortex, and parathyroid glands. *Int J Surg Pathol.* 2014;22(1):33–36.
62. Grani G, Lamartina L, Durante C, Filetti S, Cooper DS. Follicular thyroid cancer and Hurthle cell carcinoma: challenges in diagnosis, treatment, and clinical management. *Lancet Diabet Endocrinol.* 2018;6(6):500–514.
63. Zavitsanos P, Amdur RJ, Drew PA, Cusi K, Werning JW, Morris CG. Favorable outcome of Hurthle Cell carcinoma of the thyroid treated with total thyroidectomy, radioiodine, and selective use of external-beam radiotherapy. *Am J Clin Oncol.* 2017;40(4):433–437.
64. Mueller-Gaertner HW, Brzac HT, Rehpenning W. Prognostic indices for tumor relapse and tumor mortality in follicular thyroid carcinoma. *Cancer.* 1991;67(7):1903–1911.
65. Foote RL, Brown PD, Garces YI, McIver B, Kasperbauer JL. Is there a role for radiation therapy in the management of Hurthle cell carcinoma? *Int J Radiat Oncol Biol Phys.* 2003;56(4):1067–1072.
66. Gasparre G, Bonora E, Tallini G, Romeo G. Molecular features of thyroid oncocytic tumors. *Mol Cell Endocrinol.* 2010;321(1):67–76.
67. Hoos A, Stojadinovic A, Singh B, Dudas ME, Leung DH, Shaha AR, et al. Clinical significance of molecular expression profiles of Hurthle cell tumors of the thyroid gland analyzed via tissue microarrays. *Am J Pathol.* 2002;160(1):175–183.
68. Máximo V, Soares P, Lima J, Cameselle-Teijeiro J, Sobrinho-Simoes M. Mitochondrial DNA somatic mutations (point mutations and large deletions) and mitochondrial DNA variants in human thyroid pathology: a study with emphasis on Hürthle cell

tumors. *Am J Pathol.* 2002;160(5):1857–1865.
69. 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 (Hürthle cell) tumours of the thyroid. *Brit J Cancer.* 2005;92(10):1892.
70. Chindris A-M, Casler JD, Bernet VJ, Rivera M, Thomas C, Kachergus JM, et al. Clinical and molecular features of Hürthle cell carcinoma of the thyroid. *J Clin Endocrinol Metabol.* 2015;100(1):55–62.
71. Corver WE, Ruano D, Weijers K, Den Hartog WC, 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.
72. de Vries MM, Celestino R, Castro P, Eloy C, Máximo V, van der Wal JE, et al. RET/PTC rearrangement is prevalent in follicular Hürthle cell carcinomas. *Histopathology.* 2012;61(5):833–843.
73. Evangelisti C, de Biase D, Kurelac I, Ceccarelli C, Prokisch H, Meitinger T, et al. A mutation screening of oncogenes, tumor suppressor gene TP53 and nuclear encoded mitochondrial complex I genes in oncocytic thyroid tumors. *BMC Cancer.* 2015;15(1):157.
74. Ganly I, Makarov V, Deraje S, Dong Y, Reznik E, Seshan V, et al. Integrated genomic analysis of Hürthle Cell cancer reveals oncogenic drivers, recurrent mitochondrial mutations, and unique chromosomal landscapes. *Cancer Cell.* 2018;34(2):256 70.e5.
75. Ganly I, Ricarte Filho J, Eng S, Ghossein R, Morris LG, Liang Y, et al. Genomic dissection of Hurthle cell carcinoma reveals a unique class of thyroid malignancy. *J Clin Endocrinol Metabol.* 2013;98(5):E962–EE72.
76. 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 Sciences.* 2007;104(21):9001–9006.
77. 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.
78. Kasaian K, Chindris A-M, Wiseman SM, Mungall KL, Zeng T, Tse K, et al. MEN1 mutations in Hürthle cell (oncocytic) thyroid carcinoma. *J Clin Endocrinol Metabol.* 2015;100(4):E611–E6E5.
79. Landa I, Ganly I, Chan TA, Mitsutake N, Matsuse M, Ibrahimpasic T, et al. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. *J Clin Endocrinol Metabol.* 2013;98(9):E1562–E15E6.
80. Qasem E, Murugan AK, Al-Hindi H, Xing M, Almohanna M, Alswailem M, et al. TERT promoter mutations in thyroid cancer: a report from a Middle Eastern population. *Endocr-Relat Cancer.* 2015;22(6):901–908.
81. van der Tuin K, Ventayol M, Corver W, Khalifa M, Ruano D, Corssmit E, et al. Targetable gene fusions identified in radioactive iodine-refractory advanced thyroid carcinoma. *Eur J Endocrinol.* 2019;1(aop).
82. Wei S, LiVolsi VA, Brose MS, Montone KT, Morrissette JJ, Baloch ZW. STK11 mutation identified in thyroid carcinoma. *Endocr Pathol.* 2016;27(1):65–69.
83. Wei S, LiVolsi VA, Montone KT, Morrissette JJ, Baloch ZW. PTEN and TP53 mutations in oncocytic follicular carcinoma. *Endocr Pathol.* 2015;26(4):365–369.
84. Corver WE, Demmers J, Oosting J, Sahraeian S, Boot A, Ruano D, et al. ROS-induced near-homozygous genomes in thyroid cancer. *Endocr-Relat Cancer.* 2018;25(1):83–97.