The Significance of Hürthle Cells in Thyroid Disease

JENNIFER CANNON

Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina, USA

Key Words. Hürthle cell • Oncocyte • Thyroid neoplasia • Hürthle cell neoplasm • Hürthle cell carcinoma

Disclosures

Jennifer Cannon: None.

Section Editor **Herbert Chen** discloses no financial relationships.

Section Editor **Stan Sidhu** discloses no financial relationships.

Reviewer "A" discloses research funding received from the Israel Cancer Association for investigation of the role of microRNA in PTC.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. On the basis of disclosed information, all conflicts of interest have been resolved.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Enumerate the variable thyroid pathological conditions in which Hürthle cells are seen and explain the significance of the findings within the appropriate clinical context.
2. Describe the various means by which Hürthle cell neoplasms may be evaluated and their value in determining the likelihood of a benign or malignant lesion.

This article is available for continuing medical education credit at CME.TheOncologist.com.

ABSTRACT

Hürthle cells (HCs) and HC change, along with the frequently employed synonyms "oncocytes/oncocyctic change" or "oxyphils/oxyphilic change," are not infrequently described on fine-needle aspiration biopsy (FNAB) reports of thyroid lesions. The description of HCs on FNAB reports may cause significant concern to the clinician; however, placing the finding in the appropriate clinical context may alleviate some anxiety. Not all oxyphilic cells are true HCs and not every aspirate containing HCs is or should be considered equivalent to an HC neoplasm (HCN). There are many benign thyroid lesions as-

sociated with HCs or HC change. For clinicians, it may be difficult to discern the significance of these findings and to determine an appropriate course of action. A skilled and experienced cytopathologist is invaluable in discriminating the subtle features that distinguish these lesions from those warranting a more aggressive approach. The diagnosis of HC carcinoma relies on histopathologic scrutiny and evidence of capsular and/or vascular invasion or metastasis to lymph nodes or distant organs. Many investigators have sought clinical, radiographic, cytological, genetic, and other factors to attempt to discriminate pre-

Correspondence: Jennifer Cannon, M.D., Wake Forest University Health Sciences, Department of General Surgery, Wake Forest University Baptist Medical Center, Medical Center Drive, Winston-Salem, North Carolina 27157, USA. Telephone: 336-716-3936; Fax: 336-716-6637; e-mail: jcannon@wakehealth.edu Received August 11, 2010; accepted for publication July 28, 2011; first published online in *The Oncologist Express* on September 30, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 <http://dx.doi.org/10.1634/theoncologist.2010-0253>

operatively between benign and malignant HCNs. To date, none have been definitively proven to be reliable. For now, because of the inability to determine the benign or malig-

nant nature of such neoplasms based on cytology alone, a surgical approach is warranted. *The Oncologist* 2011;16:1380–1387

INTRODUCTION

Thyroid nodules are exceedingly common, occurring in 5%–8% of the clinical population, increasing to 15%–67% when high-frequency ultrasound is employed. There is an ~50% prevalence in autopsy series [1, 2]. A multitude of pathological conditions of the thyroid are manifest by nodules. These range from hyperplastic or adenomatous (non-neoplastic) nodules, including nodular goiter and chronic lymphocytic thyroiditis (CLT), to encapsulated neoplasms such as benign follicular adenomas (FAs), to malignant neoplastic disease, including well-differentiated thyroid cancers, medullary thyroid cancer (MTC), and metastases from various sources. Nodules may be discovered on routine physical exam, when they begin to cause symptoms of compression, or increasingly, as incidental findings on imaging studies performed for other reasons.

Fine-needle aspiration biopsy (FNAB) has become an invaluable tool and the gold standard in the evaluation of thyroid nodules. There is tremendous variability reported in the results; it is crucial that one understands the value of this tool at one's own institution [3]. Among the descriptions employed by cytopathologists in the interpretation of FNAB are those of Hürthle cell neoplasm (HCN), Hürthle cell (HC) change, and variations thereof. The dilemma facing the clinician is how to proceed from there. What findings are significant and warrant surgical evaluation/intervention? Which may be observed? The purpose of this review is to clarify those features that define HCs, describe the various thyroid conditions associated with HCs, and review some of the difficulties and controversies encountered by those charged with the diagnosis and care of patients with HC lesions.

HISTORICAL BACKGROUND

In 1894, Karl Hürthle described an intrafollicular cell of the thyroid gland found in normal canines, while acknowledging that Baber had previously described this same cell in other laboratory animals. What Hürthle described, however, were the parafollicular C cells, not those now associated with his name. The cell now known as the HC was actually described in 1898 by Max Askanazy in patients with Graves' disease. James Ewing, in his seminal text *Neoplastic Diseases*, described a thyroid carcinoma with cells containing finely granular, eosinophilic cytoplasm and suggested that they might be "hy-

pertrophic Hürthle cells." Langhans had, in fact, previously described the tumor discussed by Ewing, in 1907; it was composed of a distinctly different cell than that described by Hürthle. Nonetheless, since at least 1928, the term "Hürthle cell" has been appended to the cells originally described by Askanazy [4–6].

The term "oncocyte" was introduced by Hamperl in 1931 to describe a virtually identical cell structure found in the salivary glands. Similar cells were also described in the parathyroid gland by Welsh, who referred to them as "oxyphilic cells." The terms oncocyte, Hürthle cell, and oxyphilic cell are now widely used interchangeably to indicate cells displaying similar, specific features, independent of anatomic location. Hürthle cell is properly used only to describe cells of thyroid follicular origin [5, 7]. The clinical significance of oncocytic change in thyroid tumors is controversial. Oncocytic thyroid tumors have historically been perceived as carrying a higher risk for malignancy, and in the case of cancer, to carry a worse prognosis than their conventional counterparts [8]. More recent evidence suggests that oncocytic thyroid neoplasms are no more aggressive than usual variants [9, 10].

WHAT IS A HÜRTHLE CELL?

Despite the historical misnomer, the term Hürthle cell is used to describe follicular-derived epithelial cells with oncocytic cytology. As stated above, they are also described as oncocytic or oxyphilic cells. An oncocyte is simply an epithelial cell with an acidophilic cytoplasm, containing a vast number of mitochondria. They are found throughout the body, including the kidney, salivary glands, and parathyroids, as well as the thyroid gland. More specifically, the HC is a large (10–15 μ), polygonal cell with distinct cell borders, abundant eosinophilic finely granular cytoplasm, a large hyperchromatic round to oval nucleus, and a prominent nucleolus. There are numerous mitochondria in the cytoplasm contributing to the cell's size and staining characteristics. Although the actual amount of cytoplasm in HCs may vary, it is generally sufficient to produce a low nuclear–cytoplasm ratio [4, 7, 9]. Ultrastructurally, when viewed via electron microscopy, the mitochondria often appear to fill the cytoplasm, to the near exclusion of other organelles. HCs contain up to 5,000 mitochondria, whereas a typical eosinophil may contain ~30. The mitochondria often show filamentous inclusions, as well as dense core gran-

Table 1. Comparison between Hürthle cell and follicular neoplasms.

Characteristic	Hürthle	Follicular
Cellular appearance	● Large, polygonal	● Small, rounded
Cytoplasm	● Eosinophilic ● Finely granular ● Low nuclear–cytoplasm ratio	● Coarsely granular or nongranular ● Pale ● May be scant
Mitochondrial content	● Dense (up to 5,000/cell)	● Low to moderate density
Nucleus	● Enlarged ● Hyperchromatic ● Prominent nucleolus	● Round to oval ● Nucleoli not prominent
Thyroglobulin	● +	● ++ to +++
Risk for malignancy	● 15%–45% (some sources, up to 65%)	● 15%–20% (some sources, up to 30%)
Route of metastasis	● Lymphatic	● Hematogenous
Iodine avidity	● Poor (~5%)	● Good (~75%)
Prognosis (malignant)	● Overall survival similar to follicular thyroid carcinoma ● Male sex, older age, tumor size effect	● 10-yr survival rate, 85%
See text for references.		

ules. The accumulation of mitochondria has been reported to be a result of alterations in the mitochondrial DNA encoding for mitochondrial enzymes, leading to proliferation through stimulation of transcription factors encoded by the nucleus [9, 11].

The World Health Organization (WHO) prefers the term oncocytic or oncocyte to Hürthle cell [12]. Oncocytic variants of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) have the typical molecular features of their conventional counterparts and, stage for stage, have similar prognoses [9, 11]. They do, however, demonstrate a lesser ability to concentrate iodine and thus are less responsive to radioactive iodine therapy. The WHO also classifies HC adenoma (HCA) and HC carcinoma (HCC) as oncocytic variants of FA and follicular cell carcinoma, respectively. Despite this, HCC is considered by many to be a distinctly separate entity by virtue of its distinct genetic profile and clinically more aggressive behavior when compared with PTC and FTC [8, 13, 14].

Not all oncocytic cells in the thyroid are true HCs. Non-HC oncocytic follicular cells contain eosinophilic cytoplasm, which is generally nongranular, in contrast to the granular cytoplasm of true HCs. They are slightly larger than a normal follicular cell and are commonly seen on FNAB results from nodular goiters and dominant hyperplastic or adenomatous nodules [9]. Oncocyte-like lesions may have, rather than abundant mitochondria, an accumulation of lysosomes, smooth endoplasmic reticulum (ER), and neurosecretory granules, or some combination thereof, resulting in deeply eosinophilic staining characteristics [7].

Some authors strongly believe that a distinction should be made between proliferations of true HCs, containing cells with the classic cytologic appearance, and smears containing this second similar, but separate, type of cell [9].

Biologically, HCs appear to be less active than typical follicular cells, demonstrating lower levels of thyroglobulin production, and HCCs have been shown to have markedly lower iodine uptake than their follicular counterparts. HCCs do, however, contain high levels of oxidative enzymes [9]. A functional thyroid-stimulating hormone receptor-adenylate cyclase system has been demonstrated in benign HCN [4] (Table 1).

THYROID PATHOLOGY ASSOCIATED WITH HCS

HCS may be found in a wide variety of conditions affecting the thyroid gland; they are not specific to any particular pathology [12]. They are commonly found in older individuals, those who have undergone thyroid irradiation, and patients with long-standing nodular goiters, Graves' disease, and CLT. The classic definition of Hashimoto's disease calls for the triad of lymphocytes, plasma cells, and HCs [9, 15].

CLT or Hashimoto's thyroiditis is, in most cases, a diffuse process, but in some instances discrete nodules may be dominant. Follicular cell metaplasia, ranging from pale pink cells with abundant cytoplasm to true HCs with the characteristic granular, deeply eosinophilic cytoplasm, is commonly seen. Reflecting the apparent need for cells to accumulate significant numbers of mitochondria over a

prolonged period of time, HC metaplasia is rarely seen in the juvenile form of CLT [16].

Although the disease entity in which Askanazy first described HCs, diffuse toxic goiter (Graves' disease), typically does not contain an abundance of HCs, they may be seen in cases of long-standing Graves' disease, in older individuals with the disease, or in patients with a history of Graves' disease who have undergone radioactive iodine ablation and subsequently develop nodular thyroid disease [9].

HCs are also seen in neoplastic diseases of the thyroid, both benign and malignant, including HCA, HCC, variants of PTC, and the oncocytic variant of MTC, among others. Oncocytic/oxyphilic change, HC change, focal or diffuse, may be described. Oxyphilic cells may be seen in metastatic renal cell carcinoma to the thyroid; however, these are not true HCs because they are not derived from thyroid follicular epithelium.

FNAB FINDINGS AND INTERPRETATION

FNAB is the gold standard in the evaluation of thyroid nodules. Whereas some cytopathologists have chiefly viewed FNAB as a triage tool, others have attempted to extend the utility of aspirates to include more specific clinical recommendations [17]. The main objective should be to identify clinically relevant nodules that unequivocally require surgery; however, FNAB may be less reliable when "a monotonous population of three-dimensional groups of follicular cells with scarce colloid is aspirated." In such cases, hyperplastic lesions and benign and malignant neoplasms are cytologically indistinct [18].

FNAB aspirates of non-neoplastic lesions are often comprised of HCs, benign follicular cells without oncocytic change, and colloid, as in the case of nodular goiter, or of HCs, aggregates of lymphocytes and dendritic cells, and benign follicular cells, as seen in CLT. In rare circumstances, FNAB of a thyroid nodule may reveal oxyphilic cells from an intrathyroidal parathyroid adenoma. The cells may be indistinguishable from HCs, with their true identity revealed only on final pathology [7].

A long-standing difficulty in thyroid cytopathology has been the significant variation in terminology used from lab to lab. This has created confusion regarding clinical decision making, created uncertainty in interpretation of results from one institution to the next, and hindered sharing of useful data among investigators. The Bethesda classification scheme was recently developed in an effort to create a more unified language for reporting the results of thyroid FNABs [12, 14, 19]. Although an in-depth discussion of these guidelines is beyond the scope of this review, readers are encouraged to read and familiarize themselves with

these guidelines. The Bethesda system appears to be gaining wider acceptance and usage; however, it is not yet universally employed. Knowing the verbiage used by the laboratory at one's institution as well as the final histopathology results associated with the initial cytology is critical to interpretation of FNAB reports and using the information in sound clinical decision making.

Beyond variations in terminology, a high degree of intraobserver variability in the interpretation of thyroid specimens has also been demonstrated. Although second review of all thyroid aspirates containing oncocytes or HCs is often impractical, liberal use at the discretion of the overseeing cytopathologist or at the request of the treating clinician may be warranted [17]. A skilled and experienced cytopathologist is irreplaceable in the interpretation of FNAB results, rendering an opinion as to the presence or absence of true HCs and whether or not the nodule of interest is sufficiently HC predominant to raise clinical concern.

Adequacy of FNAB has been variably defined as a minimum of six groups of follicular cells containing ≥ 10 (benign) cells per group on one or more slides, five to six groups of follicular cells with 10–20 cells per group on at least two slides, and six groups on at least two of six aspirates, etc. [20]. The Bethesda guidelines specifically define a satisfactory specimen as containing six groups of benign follicular cells, each group composed of ≥ 10 cells. Exceptions to this requirement do exist, as in the case of smears containing abundant colloid and few cells, which may be interpreted as benign [12, 14, 19]. The definition of what constitutes an HCN has not, however, been so discretely delineated. Some labs interpret an aspirate containing 50% HCs as suspicious for HCN, whereas others require a far more stringent 90%. A commonly used definition, and that preferred by the author, is an aspirate containing $>75\%$ HCs with little or no background colloid; the nuclear features of PTC must be absent [9]. It has been suggested that a small number of HCNs may be missed by a more stringent ($>50\%$) requirement [6, 21], and others have shown that more aggressive neoplasms are more cellular, up to 90%–100% HCs in one report [6]. Using the 75% criterion thus selects for those nodules more likely to harbor malignancy. Because it is impossible to identify the presence or absence of a capsule on FNAB, all lesions meeting these criteria should be treated as HCNs and patients should undergo thyroid lobectomy for diagnosis, with the knowledge that a substantial percentage will prove to be non-neoplastic (15%–25%, up to 35% in some series) on final histology. Malignancy will be found in up to 30% (45%–64% in some series, reflecting tertiary referral patterns) [3, 4, 13, 22], and the remaining nodules will be benign adenomas [14].

Alaadeen and coinvestigators sought to identify factors,

clinical and/or cytopathological, that might distinguish neoplastic from non-neoplastic lesions in patients with FNAB aspirates containing a predominance of HCs. In that series, 17 of 45 (38%) patients had non-neoplastic HC nodules. The FNAB from non-neoplastic HC nodules did not show any specific features that could distinguish them from HCNs. The only cytomorphologic features associated more frequently with neoplastic disease were extensive overall cellularity, absent colloid, and extensive HC cellularity; no feature reliably excluded neoplasia [23]. This underscores the difficulty in determining the proper course of action when “HC hyperplasia” versus “HCN” is reported on FNAB reports—there is no cytopathologic feature that can easily differentiate the two. The clinical context, individual patient risk profile, and clinician judgment must determine the proper course of action.

In a provocative study, Renshaw elaborated a set of FNAB cytology criteria designed to improve the specificity of an HCN diagnosis without sacrificing sensitivity. Although not all HCCs could readily be distinguished from HCAs, some HCAs, by virtue of not meeting *any* of the criteria, were felt to be reliably diagnosed as benign. He concluded that, by restricting the criteria used in the diagnosis of HCN to those consistently seen in HCC, for example, making HCC the “gold standard,” the specificity may be increased and patients with clearly benign lesions may be spared surgery [24]. These criteria were subjected to validation by Wu et al. [25], with good correlation. Further studies are warranted to better validate these findings.

BENIGN VERSUS MALIGNANT

In the past, it was believed by some authors that every HCN carried malignant potential and thus warranted total thyroidectomy [22]. Later studies found that the histological diagnosis was consistent with the clinical behavior of the tumors and the long-term risk for recurrence [8, 26, 27]. The ability to distinguish benign from malignant HC lesions of the thyroid preoperatively is something of a “holy grail” among those involved in the diagnosis and management of such nodules. The current definition of a malignant HCN depends on capsular and/or vascular invasion, and the presence of metastasis. This cannot be determined by cytologic evaluation and relies on histological examination of a surgically resected specimen. Frozen section evaluation has been shown to be of little use in the intraoperative evaluation of these lesions. Among its limitations, frozen section evaluation is compromised by sampling error, variable thickness, irregularity of the capsule, and freezing artifacts [28, 29].

Clinical criteria to guide surgeons’ preoperative decision making and determine the extent of surgery have been

sought by numerous investigators [13, 30–33]. Among the clinical parameters evaluated, the most commonly identified factors predicting malignancy have been older age and size of tumor, yet these are not consistent across series, particularly size [4, 13, 22, 25, 26, 32, 33]. Male sex has been reported to be more highly associated with malignancy; however, this too has been inconsistent [13, 30–32].

Ultrasound has become a widely recognized tool in the diagnosis and management of nodular thyroid disease. A number of sonographic characteristics have been reported to be more frequently associated with malignant nodules. Among these are hypoechogenicity, microcalcifications, ill-defined borders, internal vascularity, and nodules that are taller than wide. Although no single feature has a high degree of accuracy in predicting malignancy, the combined presence of hypoechogenicity, microcalcifications, and irregular borders in the same nodule has been shown to correlate with a 30-fold higher risk for malignancy in well-differentiated thyroid cancer [34–36]. Maizlin et al. [37] attempted to apply these criteria to lesions reported as HCNs using FNAB. Final histological evaluation revealed that there was no characteristic sonographic appearance that could readily distinguish a benign from a malignant tumor [37]. Ultrasound may be most useful in HCN diagnosis when sonographically abnormal lymph nodes are identified, suggesting metastatic disease, as reported by Pisanu et al. [33]. Preoperative FNAB of these nodes accompanied by measurement of the thyroglobulin level of the specimen can increase the accuracy of a malignant diagnosis and greatly aid preoperative planning [36].

Other imaging modalities, including computed tomography, magnetic resonance imaging, 18-fluorodeoxyglucose-positron emission tomography (FDG-PET), and ⁹⁹Tc-sestamibi (MIBI) scan are often the means by which thyroid “incidentalomas” are initially detected. HC lesions often appear especially bright on MIBI scans because of their high mitochondrial content [19]. Pisanu’s group found that a positive MIBI scan was strongly associated with HCN, but was of no utility in discriminating benign from malignant lesions [33]. The 2009 American Thyroid Association Guidelines for Management of Thyroid Nodules suggest that nodules that are positive on PET may demonstrate a higher rate of malignancy and should undergo FNAB, regardless of size [2]. Although not recommended for routine investigation in the initial evaluation of thyroid nodules, these modalities may be useful in identifying metastases associated with lesions that do not concentrate iodine, as in the case of most HCCs [29].

Flow cytometry and the assessment of cytological atypia have been examined as well. Cytological atypia may include necrosis, nuclear pleomorphism/crowding, greater

mitoses, and/or irregular nuclei with hyperchromasia [32]. Cytomorphologic criteria alone have not been widely shown to be helpful in distinguishing between benign and malignant HCNs; nuclear atypia, multinucleation, mitoses, and cellular pleomorphism are not sufficient and reliable determinants of malignant behavior [4, 9, 13, 18]. Benign oncocytic nodules found in Graves' disease, long-standing nodular goiter, and CLT frequently show cellular atypia and marked nuclear pleomorphism. Flow cytometry has been shown, in some studies, to provide prognostic information in histologically confirmed cancers; those with aneuploid DNA appear to behave more aggressively than those that are diploid. However, benign adenomas may demonstrate aneuploidy and cancers may be diploid. Neither flow cytometry nor analysis of cellular atypia has been proven to be able to discriminate between benign and malignant HCNs [9, 29, 38].

Molecular markers and immunohistochemistry (IHC) are promising tools in the preoperative diagnosis of HCC. Ki67, a marker of cell proliferation, and cyclin D1, a cell cycle promoter, are expressed at higher levels in HCCs than in HCAs. Bcl-2, on the other hand, an antiapoptotic protein, is downregulated in HCC [31]. Troncone et al. [18] evaluated the usefulness of a panel of IHC markers, D-type cyclins D1 and D3, to determine their diagnostic performance in the assessment of FNAB samples suspicious for HCN. D-type cyclin upregulation, particularly of D3, was found to be a consistent feature of malignant lesions. The rate of false-positive diagnosis was lower when both markers were used. Using these methods in the context of a multidisciplinary assessment may improve the diagnostic accuracy [18]. Other markers examined by investigators include MIB1, p53, galectin, topoisomerase II, and laminin; as yet, none are definitive for discrimination between benign and malignant HCNs. Tsybrovskyy and Rößmann-Tsybrovskyy proposed the theory that oncocytic change is not just an accumulation of mitochondria, but a complex, special reorganization of all major cell organelles potentially associated with neoplasia and malignancy pathways. They found that significantly greater ER (which also stains deeply eosinophilic) was strongly associated with inflammatory processes, whereas neoplasia was characterized by significantly more mitochondria. Their findings suggest that IHC for mitochondria and ER may alter the significance of what is traditionally thought of as "oncocytic change." This requires further study and should be considered in the context of tumor stage, invasion, and other validated factors [10].

MicroRNA (miRNA) analysis is yet another emerging tool in the quest to differentiate benign from malignant lesions. Kitano et al. [39] examined the role of these small,

noncoding RNAs that typically serve as regulatory molecules. Microarray analysis was used to perform miRNA profiling on thyroid tissue samples in order to identify those miRNAs that were dysregulated between benign and malignant histologies, focusing on those histologies difficult to distinguish on FNAB. The group included hyperplastic nodules/multinodular goiter, HCA, FA, HCC, FTC, PTC, and follicular variant PTC in their analysis, as well as normal thyroid tissue. Thirty-four miRNAs were found to be differentially expressed between benign and malignant samples. This was statistically significant ($p < .05$) and validated in 25 of 34 miRNAs via quantitative real-time polymerase chain reaction. Further study, particularly, validation in additional tumor samples with FNAB samples suggesting an indeterminant lesion, such as follicular neoplasia (FN) or HCN, is warranted [39].

MANAGEMENT

Clinicians must make thoughtful decisions regarding patients presenting with thyroid nodules and FNAB aspirates containing HCs. Once again, being familiar with the language commonly used by one's institution and referring laboratories cannot be emphasized enough. Equally important is the historical resultant final pathology based on those FNAB reports. For example, in one institution, an FNAB report of "suspicious for X carcinoma" may carry a $\geq 90\%$ rate of malignancy on final histology, whereas in another the rate may be closer to 60%–70%. This information may greatly affect operative planning. FNAB specimens consistent with FN or HCN are variously categorized as indeterminate, suspicious, cellular, or, in the Bethesda system, category 4. They represent $\sim 20\%$ of all FNAB results in patients with thyroid nodules. Of these, $\sim 10\%$ are HCNs. As previously stated, although referral patterns may affect malignancy rates, historically, 15%–30% of patients with a nodule and FNAB results consistent with FN or HCN are subsequently diagnosed with a malignant lesion [32].

Not all lesions with HCs on FNAB require surgical intervention. The importance of clinical context must be emphasized. Aspirates with scattered HCs, macrofollicular architecture, or abundant, watery colloid, and those seen in the context of CLT without dominant nodules, as well as those that do not meet the criteria for HCN ($< 75\%$ HCs) can generally be observed with surveillance ultrasonography and repeat FNAB when indicated.

Upon diagnosis of HCN by FNAB, thyroid lobectomy is warranted for definitive diagnosis. When the final histological exam reveals HCC, completion thyroidectomy is performed within either a few days of the initial procedure or 3 months later. In some cases, an initial total thyroidectomy may be preferable:

1. A history of prior head and/or neck irradiation often predisposes patients to multifocal disease, including coexisting PTC. These patients should generally undergo total thyroidectomy as an initial operation because the incidence of carcinoma approaches 40% [29].

2. Patients with nodules in the contralateral lobe may be considered for a single-stage total thyroidectomy.

3. Although size alone cannot be directly correlated with malignancy, larger nodules (those >4 cm) may be more likely to be carcinomas on final histology. This factor is a relative indication, which on an individualized basis may be used to identify those patients who might benefit from a total thyroidectomy at first operation [4, 30, 31].

4. Patients who have a high level of concern or anxiety about the possibility of malignancy or desire to avoid a second operative procedure are also justifiably served by undergoing a single total procedure at the outset. These patients should be informed that this is a more aggressive approach and will, in 70%–80% of cases, be done for a benign process. They should be fully informed of the risks associated with the procedure [29].

Malignant HCNs do require aggressive surgery, because they are poorly responsive to chemotherapy, do not concentrate iodine, and are generally not radiosensitive. When metastases are present at the time of diagnosis, aggressive surgical approaches do not appear to have much influence on the long-term outcome and are chiefly palliative, underscoring the need to perform timely FNAB of solid thyroid nodules [40]. Studies have shown that HC tumors do demonstrate the ability to synthesize thyroglobulin and may stain positive with IHC techniques; thus, some investigators suggest evaluating each case on an individual basis post-thyroidectomy and treating with a therapeutic dose of ^{131}I , should radioactive iodine uptake be evident [4]. As a general rule, however, only 5%–10% of HCC take up ^{131}I , in contrast to ~75% of FTCs [29]. External-beam radiation has been used with success in the palliation of bone metastases, but it has not been shown to be effective for residual neck and soft tissue disease and metastases [4].

CONCLUSION

HCs may be found in lesions across the spectrum of thyroid disease. The significance of HCs in thyroid pathology is currently uncertain. Although surgery may not always be mandatory when an FNAB specimen contains HCs, a clear concern is that of missing a malignant lesion by abstaining from surgery [6]. Although the mere presence of HCs or HC change in an FNAB smear should not immediately trigger clinical worry and perhaps an unnecessary surgical referral, clinical context and an appreciation for the variety of findings associated with oncocytes may help guide the clinician to appropriate clinical follow-up [9].

Because HC lesions present a particularly challenging component of thyroid pathology, the cornerstone critical to managing HC nodules is a highly skilled, experienced pathologist [27]. Equally critical is understanding the nomenclature and phraseology commonly used in one's own institution and referring laboratories; unless and until all pathology labs adopt a uniform language and common standards for evaluating all aspirates, one must interpret data within the context of one's practice. Although the presence of vascular or capsular invasion on permanent histology may easily be recognized, no unequivocal cytological parameters currently exist that can define carcinoma before or during thyroidectomy. Likewise, there are no specific, reliable clinical factors to distinguish HCA from HCC. The safest course of action is for all patients with a diagnosis of HCN, made by a cytopathologist with adequate expertise and using accepted guidelines and criteria, to undergo surgical excision in order to obtain a definitive diagnosis [33].

ACKNOWLEDGMENTS

The author wishes to acknowledge Richard B. Cannon, M.D., of the Division of Endocrinology, Intermountain Heath Care, Salt Lake City, UT (ret.), for his kind assistance in the review and preparation of this manuscript.

REFERENCES

- Yeung MJ, Serpell JW. Management of the solitary thyroid nodule. *The Oncologist* 2008;13:105–112.
- Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;11:1167–1214.
- Mijovic T, Rochon L, Gologon O et al. Fine-needle aspiration biopsies in the management of indeterminate follicular and Hürthle cell thyroid lesions. *Otolaryngol Head Neck Surg* 2009;140:715–719.
- McLeod MK, Thompson NW. Hürthle cell neoplasms of the thyroid. *Otolaryngol Clin North Am* 1990;23:441–452.
- Caturegli P, Ruggere C. Karl Hürthle? Now, who was he? *Thyroid* 2005;15:121–123.
- Kauffman PR, Dejax C, de Latour M et al. The meaning and predictivity of Hürthle cells in fine needle aspiration cytology for thyroid nodular disease. *Eur J Surg Oncol* 2004;30:786–789.
- Wakely PE Jr. Oncocytic and oncocyte-like lesions of the head and neck. *Ann Diagn Pathol* 2008;12:222–230.
- Carcangiu ML, Bianchi S, Savino D et al. Follicular Hürthle cell tumors of the thyroid gland. *Cancer* 1991;68:1994–1953.
- Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hürthle (oncocytic)

- cell and its associated pathologic conditions: A surgical pathology and cytopathology review. *Arch Pathol Lab Med* 2008;132:1241–1250.
- 10 Tsybrovskyy O, Rößmann-Tsybrovskyy M. Oncocytic versus mitochondrion-rich follicular thyroid tumors: Should we make a difference? *Histopathology* 2009;55:665–682.
  - 11 Sobrinho-Simões M, Maximo V, Castro IV et al. Hürthle (oncocytic) cell tumors of thyroid: Etiopathogenesis, diagnosis and clinical significance. *Int J Surg Pathol* 2005;13:29–35.
  - 12 Baloch ZW, LiVolsi VA, Asa SL et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: A synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagn Cytopathol* 2008;36:425–437.
  - 13 Giorgadze T, Rossi ED, Fadda G et al. Does fine-needle aspiration diagnosis of “Hürthle-cell neoplasm/follicular neoplasm with oncocytic features” denote increased risk of malignancy? *Diagn Cytopathol* 2004;31:307–312.
  - 14 Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 2009;19:1159–1165.
  - 15 Sidhu S. Hürthle cell neoplasm of the thyroid gland. *ANZ J Surg* 2008;78:115.
  - 16 LiVolsi VA. The pathology of autoimmune thyroid disease: A review. *Thyroid* 1994;4:333–339.
  - 17 Stelow EB, Woon C, Atkins KA et al. Intraobserver variability with the interpretation of thyroid FNA specimens showing predominantly Hürthle cells. *Am J Clin Pathol* 2006;126:580–583.
  - 18 Troncone G, Volante M, Iaccarino A et al. Cyclin D1 and D3 overexpression predicts malignant behavior in thyroid fine-needle aspirates suspicious for Hürthle cell neoplasms. *Cancer* 2009;117:522–529.
  - 19 Layfield LJ, Cibas ES, Baloch Z. Thyroid fine needle aspiration cytology: A review of the National Cancer Institute state of the science symposium. *Cytopathology* 2010;21:75–85.
  - 20 Renshaw AA. Evidence-based criteria for adequacy in thyroid fine-needle aspiration. *Am J Clin Pathol* 2002;118:518–521.
  - 21 Elliott DD, Pitman MB, Bloom L et al. Fine-needle aspiration biopsy of Hürthle cell lesions of the thyroid gland: A cytomorphologic study of 139 cases with statistical analysis. *Cancer* 2006;108:102–109.
  - 22 Gundry SR, Burney RE, Thompson NW et al. Total thyroidectomy for Hürthle cell neoplasm of the thyroid. *Arch Surg* 1983;118:529–532.
  - 23 Alaudeen DI, Khiyami A, McHenry CR. Fine-needle aspiration biopsy specimen with a predominance of Hürthle cells: A dilemma in the management of nodular thyroid disease. *Surgery* 2005;138:650–657.
  - 24 Renshaw AA. Hürthle cell carcinoma is a better gold standard than Hürthle cell neoplasm for fine-needle aspiration of the thyroid: Defining more consistent and specific cytologic criteria. *Cancer* 2002;96:261–266.
  - 25 Wu HH, Clouse J, Ren R. Fine-needle aspiration cytology of Hürthle cell carcinoma of the thyroid. *Diagn Cytopathol* 2008;36:149–154.
  - 26 Gosain AK, Clark OH. Hürthle cell neoplasms: Malignant potential. *Arch Surg* 1984;119:515–519.
  - 27 Grant CS, Barr D, Goellner JR et al. Benign Hürthle cell tumors of the thyroid: A diagnosis to be trusted? *World J Surg* 1988;12:488–495.
  - 28 LiVolsi VA, Baloch ZW. Use and abuse of frozen section in the diagnosis of follicular thyroid lesions. *Endocr Pathol* 2005;16:285–293.
  - 29 McHenry CR, Sandoval BA. Management of follicular and Hürthle cell neoplasms of the thyroid gland. *Surg Oncol Clin N Am* 1998;7:893–910.
  - 30 Chen H, Nicol TL, Zeiger MA et al. Hürthle cell neoplasms of the thyroid: Are there factors predictive of malignancy? *Ann Surg* 1998;227:542–546.
  - 31 Zhang YW, Greenblatt DY, Repplinger D et al. Older age and larger tumor size predict malignancy in Hürthle cell neoplasms of the thyroid. *Ann Surg Oncol* 2008;15:2842–2846.
  - 32 McHenry CR, Thomas SR, Slusarczyk SJ et al. Follicular or Hürthle cell neoplasm of the thyroid: Can clinical factors be used to predict carcinoma and determine extent of thyroidectomy? *Surgery* 1999;126:798–804.
  - 33 Pisanu A, Sias L, Uccheddu A. Factors predicting malignancy of Hürthle cell tumors of the thyroid: Influence on surgical treatment. *World J Surg* 2004;28:761–765.
  - 34 Kim EK, Park CS, Chung WY et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. *AJR Am J Roentgenol* 2002;178:687–691.
  - 35 Lew JI, Rodgers SE, Solorzano CC. Developments in the use of ultrasound for thyroid cancer. *Curr Opin Oncol* 2010;22:11–16.
  - 36 Lew JI, Solorzano CC. Use of ultrasound in the management of thyroid cancer. *The Oncologist* 2010;15:253–258.
  - 37 Maizlin ZV, Wiseman SM, Vora P et al. Hürthle cell neoplasms of the thyroid: Sonographic appearance and histologic characteristics. *J Ultrasound Med* 2008;27:751–757.
  - 38 Nguyen GK, Husain M, Akin MR. Cytodiagnosis of benign and malignant Hürthle cell lesions of the thyroid by fine-needle aspiration biopsy. *Diagn Cytopathol* 1999;20:261–265.
  - 39 Kitano M, Rahbari R, Patterson EE et al. Expression profiling of difficult-to-diagnose thyroid histologic subtypes shows distinct expression profiles and identify candidate diagnostic microRNAs. *Ann Surg Oncol* 2011 May 7 [Epub ahead of print].
  - 40 Ahmed M, Bin Yousif H, Greer W et al. Hürthle cell neoplasm of the thyroid gland. *ANZ J Surg* 2008;78:139–143.