# Malignancy Risk for Solitary and Multiple Nodules in Hürthle Cell–Predominant Thyroid Fine-Needle Aspirations: A Multi-Institutional Study

Kristine S. Wong, MD[1]; Vickie Y. Jo, MD [1]; Alarice C. Lowe, MD[1]; William C. Faquin, MD, PhD[2]; Andrew A. Renshaw, MD [3]; Akeesha A. Shah, MD[4]; Michael H. Roh, MD, PhD[5]; Edward B. Stelow, MD[4]; and Jeffrey F. Krane, MD, PhD [1]

**BACKGROUND:** Hürthle cell metaplasia is common in hyperplastic nodules, particularly within the setting of lymphocytic thyroiditis (LT). The Bethesda System for Reporting Thyroid Cytopathology indicates that it is acceptable to classify Hürthle cell–predominant fine-needle aspiration (HC FNA) specimens as atypia of undetermined significance (AUS) rather than suspicious for a Hürthle cell neoplasm (HUR) within the setting of multiple nodules or known LT. The goal of the current study was to address whether this approach is justified. **METHODS:** HC FNA specimens were identified and correlated with ultrasound and surgical pathology reports if available. Multinodularity was determined based on findings on macroscopic examination if imaging results were unavailable. **RESULTS:** A total of 698 HC FNA specimens were identified, including 576 resected nodules, 455 of which (79%) were benign. The overall risk of malignancy for HUR was 27%, whereas the risk of malignancy for AUS was 10%. The mean size of the benign nodules was 2.1 cm on surgical resection specimens, with multiple nodules noted in 293 cases (64%) and histologic LT noted in 116 cases (25%). The mean size of the malignant nodules was 2.8 cm, with multiple nodules and histologic LT noted in 74 cases (61%) and 22 cases (18%), respectively. The malignancy rate did not differ between solitary or multiple nodules ($P = .52$) or in the presence or absence of LT ($P = .12$). However, size did significantly differ between malignant and benign nodules ($P < 0.01$). **CONCLUSIONS:** The malignancy rate did not differ significantly in the presence of multiple nodules or LT, although the latter demonstrated a statistical trend. A diagnosis of AUS over HUR based solely on the presence of multinodularity is not warranted. ***Cancer Cytopathol* 2020;128:68-75**.
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**KEY WORDS:** atypia of undetermined significance (AUS); fine-needle aspiration (FNA); follicular lesion of undetermined significance (FLUS); Hürthle cell; malignancy risk; multinodularity; thyroid.

## INTRODUCTION

Hürthle cells are modified thyroid follicular cells that demonstrate oncocytic change, resulting in abundant eosinophilic granular cytoplasm due to the presence of numerous mitochondria.[1] They often are associated with enlarged, round nuclei and central prominent nucleoli. Although oncocytic/Hürthle cell change initially was thought to be secondary to senescence, it now is believed to be a metaplastic change occurring in response

**Corresponding Author:** Jeffrey F. Krane, MD, PhD, Department of Pathology, David Geffen School of Medicine, University of California at Los Angeles, 10833 LeConte Ave, Los Angeles, CA 90095 (jkrane@mednet.ucla.edu).

Alarice C. Lowe's current address: Department of Pathology, Stanford University, Stanford, California

Akeesha A. Shah's current address: Department of Pathology, Cleveland Clinic, Cleveland, Ohio

Michael H. Roh's current address: Department of Pathology, Mayo Clinic, Rochester, Minnesota

Jeffrey F. Krane's current address: Department of Pathology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[1]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [3]Department of Pathology, Miami Baptist Hospital, Miami, Florida; [4]Department of Pathology, University of Virginia Medical Center, Charlottesville, Virginia; [5]Division of Cytopathology, Department of Pathology, University of Michigan, Ann Arbor, Michigan

**Received:** September 17, 2019; **Revised:** October 15, 2019; **Accepted:** October 29, 2019

Published online November 21, 2019 in Wiley Online Library (wileyonlinelibrary.com)

**DOI:** 10.1002/cncy.22213, wileyonlinelibrary.com

to cellular stress or changes in the microenvironment.[1] Hürthle cell metaplasia may be observed in a variety of nonneoplastic conditions such as autoimmune thyroiditis (including Hashimoto thyroiditis and Graves disease) and multinodular hyperplasia, although it also can be noted in both benign and malignant neoplasia.

Given this lack of specificity of Hürthle cell metaplasia, the accurate diagnosis of Hürthle cell–predominant fine-needle aspiration (HC FNA) specimens can be extremely problematic. Many cytologic features have been proposed for distinguishing nonneoplastic Hürthle cell nodules from neoplastic nodules as well as benign from malignant nodules, although to the best of our knowledge no criteria have been widely accepted. These include cellularity,[2-5] the amount of colloid,[2-4,6-8] architecture (ie, macrofollicular sheets, crowded groups, singly dispersed cells),[3,5,7,8] and nuclear pleomorphism or "dysplasia,"[2,3,5-9] among others. Given the inconsistency of cytologic features in the evaluation of HC FNA, it also has been suggested in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) that clinicopathologic correlation can aid in evaluation. Specifically, TBSRTC states that it is acceptable to classify HC FNA as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) rather than suspicious for a Hürthle cell neoplasm (HUR) within the setting of multiple nodules or known lymphocytic thyroiditis (LT).[10] The goal of the current study was to address whether this approach is justified.

## MATERIALS AND METHODS

### *Study Population and Data Acquisition*

Approval from the institutional review board of each participating institution was obtained. A search of HC FNA specimens was performed at each institution. Thyroid FNA cytologic preparations varied across institutions as well as within individual institutions (ie, due to operator preference), ranging from the routine use of both smear preparations (Diff-Quick staining or Papanicolaou staining) and liquid-based preparations to the use of only 1 method. Cytologic diagnoses and patient demographics were recorded for each case. HC FNA specimens were categorized using TBSRTC with the following diagnostic categories: benign, AUS, HUR, suspicious for malignancy (SUS), and malignant.

When available, nodule size and the presence or absence of multiple nodules were documented based on ultrasound reports. Surgical pathology reports from cases with surgical follow-up were reviewed. Multinodularity was determined by findings on macroscopic examination if imaging results were unavailable. The histologic diagnosis, including the presence of LT, also was recorded for each case.

Surgical pathology diagnoses were classified using a binary system (ie, benign or malignant). All cases in the current study predated the introduction of the noninvasive follicular thyroid neoplasm with papillary-like nuclear features category, and cases that had been diagnosed as follicular variant of papillary thyroid carcinoma (PTC) or PTC in which the subtype was not specified (PTC, NOS) were not reclassified. These cases were included in the malignant category for the purposes of the current study, because the goal was to differentiate benign lesions from those that would require surgical resection within the setting of multinodularity.

### *Statistical Analysis*

A Student $t$ test or Fisher exact test was used to compare differences in continuous and categorical variables, respectively (Prism 5; GraphPad, La Jolla, California). For all statistical methods, $P$ values $<.05$ were considered to be statistically significant.

## RESULTS

### *Cohort Characteristics*

Overall, a total of 698 HC FNA specimens from 677 nodules were identified. The FNA diagnosis was benign in 12 cases (2%), AUS in 275 cases (39%), HUR in 407 cases (58%), SUS in 3 cases (<1%), and malignant in 1 case (<1%). A total of 576 nodules (85%) were surgically resected. Characteristics of resected and unresected cases were compared in a subset of cases for which sufficient information for the unresected nodules was available from the participating institutions (Table 1). Patients who did not undergo surgical resection were more likely to be older ($P = .021$) and to have a preceding diagnosis of benign or AUS ($P = .011$ and $P = .0075$, respectively), whereas those with a preceding HUR diagnosis were more likely to undergo surgical resection ($P = .0017$). There was no significant difference noted between resected and unresected cases with regard to the ultrasonographic size of the nodule, the presence of multinodularity, or the presence of multiple HC nodules sampled on FNA.

**TABLE 1.** Clinicopathologic Characteristics of Resected Versus Unresected Nodules[a]

| Characteristic | Resected Nodules N = 309[a] | Unresected Nodules N = 93[a] | *P* |
|---|---|---|---|
| Sex, no. (%) | | | |
| Female | 237 (79) | 75 (82) | .77 |
| Male | 62 (21) | 17 (18) | |
| Age, y | | | |
| Mean | 55 | 59 | .021 |
| Range | 19-88 | 14-87 | |
| FNA diagnosis, no. (%) | | | |
| Benign | 1 (<1) | 4 (4) | .011 |
| AUS | 110 (36) | 48 (52) | .0075 |
| HUR | 194 (63) | 41 (44) | .0017 |
| SUS | 3 (1) | 0 (0) | 1.0 |
| Malignant | 1 (<1) | 0 (0) | 1.0 |
| Mean tumor size on ultrasound, cm | 2.4 | 2.3 | .39 |
| Nodularity, no. (%)[b] | | | |
| Multiple | 202 (66) | 52 (65) | .89 |
| Single | 103 (34) | 28 (35) | |
| HC FNA of >1 nodule, no. (%) | 10 (3) | 1 (1) | .47 |

Abbreviations: AUS, atypia of undetermined significance; FNA, fine-needle aspiration; HC FNA, Hürthle cell–predominant fine-needle aspiration; HUR, suspicious for a Hürthle cell neoplasm; SUS, suspicious for malignancy.
[a]Only information from a subset of unresected cases was available for comparison.
[b]Of the patients for whom ultrasound findings were available.

**TABLE 2.** Clinicopathologic Characteristics of All Resected Nodules

| Characteristic | All Resected Nodules N = 576 | Benign N = 455 | Malignant[a] N = 121 | *P* |
|---|---|---|---|---|
| Sex, no. (%) | | | | |
| Female | 462 (82)[b] | 368 (83)[b] | 94 (78) | .23 |
| Male | 104 (18)[b] | 77 (17)[b] | 27 (22) | |
| Age, y | | | | |
| Mean | 54 | 54 | 55 | .47 |
| Range | 19-88 | 19-88 | 15-87 | |
| FNA diagnosis | | | | |
| Benign | 7 (1) | 5 (1) | 2 (2) | .64 |
| AUS | 210 (36) | 189 (42) | 21 (17) | <.01 |
| HUR | 355 (62) | 260 (57) | 95 (79) | <.01 |
| SUS | 3 (<1) | 1 (<1) | 2 (2) | .12 |
| Malignant | 1 (<1) | 0 (0) | 1 (1) | .21 |
| HC FNA of >1 nodule, no. (%) | 10 (2) | 10 (2) | 0 (0) | .13 |
| Mean tumor size on ultrasound, cm | 2.5 | 2.3 | 2.8 | <.01 |
| Mean macroscopic tumor size, cm | 2.2 | 2.1 | 2.8 | <.01 |
| Nodularity, no. (%)[c] | | | | |
| Multiple | 367 (64) | 293 (64) | 74 (61) | .52 |
| Single | 209 (36) | 162 (36) | 47 (39) | |
| LT, no. (%) | | | | |
| Present | 138 (24) | 116 (25) | 22 (18) | .12 |
| Absent | 438 (76) | 339 (75) | 99 (82) | |
| Concurrent MN and LT, no. (%) | | | | |
| Present | 84 (15) | 68 (15) | 16 (13) | .77 |
| Absent | 492 (85) | 387 (85) | 105 (87) | |

Abbreviations: AUS, atypia of undetermined significance; FNA, fine-needle aspiration; HC FNA, Hürthle cell–predominant fine-needle aspiration; HUR, suspicious for a Hürthle cell neoplasm; LT, lymphocytic thyroiditis; MN, multinodularity; SUS, suspicious for malignancy.
*P* values were based on a comparison of benign and malignant nodules.
[a]All nonbenign nodules were included in this group, including those cases previously diagnosed as follicular variant of papillary thyroid carcinoma.
[b]Ten patients had 2 different nodules with a preceding HC FNA.
[c]Multinodularity was determined based on ultrasound or macroscopic findings.

The clinicopathologic features of all 576 cases that underwent surgical resection are summarized in Table 2. Of the resected nodules, 455 (79%) were classified as benign and 121 (21%) were classified as malignant. Sonographic assessment of multinodularity was available in 342 resected nodules overall (59%), including 261 of 455 benign nodules (57%) and 81 of 121 malignant nodules (67%). Macroscopic assessment of multinodularity was available in the remaining cases. The incidence of multinodularity was not found to be significantly different

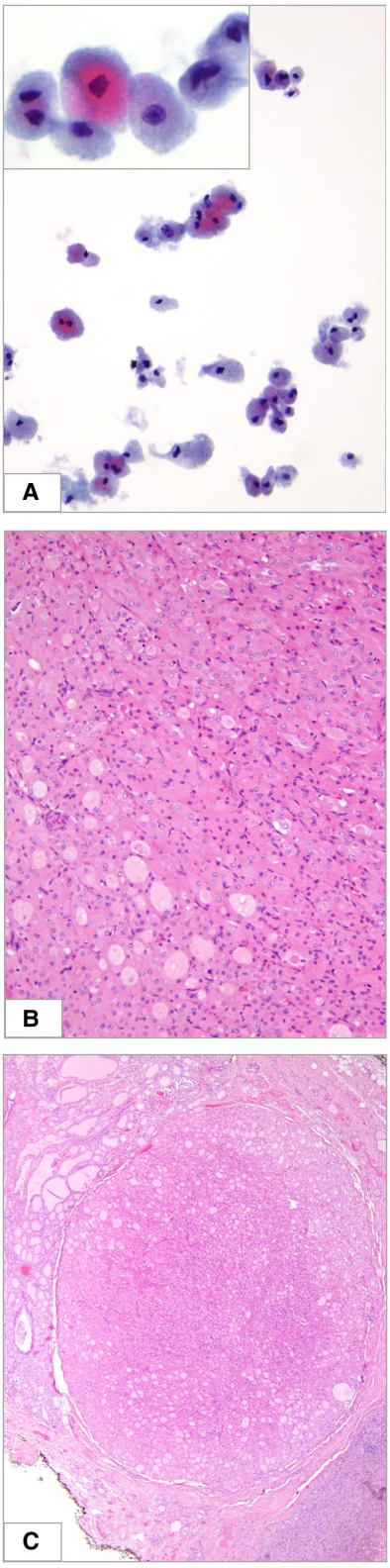


**Figure 1.** Example of a benign nodule in the current study cohort. (A) The preceding fine-needle aspiration specimen had abundant Hürthle cells that were singly dispersed and in clusters. (B and C) The surgical resection specimen demonstrated an adenomatous nodule with Hürthle cell change.

between nodules with sonographic or macroscopic assessment (65% and 62%, respectively; $P = .48$).

### *Benign Nodules*

Of the 445 patients with benign nodules, 368 (83%) were female and 77 (17%) were male. The mean age of the patients was 54 years (range, 19-88 years). The preceding FNA diagnosis was benign in 5 cases (1%), AUS in 189 cases (42%), HUR in 260 cases (57%), SUS in 1 case (<1%), and malignant in none of the cases (0%). All 10 patients who had >1 nodule with a preceding HC FNA specimen were found to have benign findings on surgical resection. The mean size of the benign nodules was 2.3 cm by ultrasound and 2.1 cm on surgical resection. Multiple nodules were identified in 293 cases overall (64%), including 167 of 261 cases (64%) for which sonographic assessment was available and 126 of 194 cases (65%) that were evaluated macroscopically. On histopathologic examination, there were 264 follicular adenomas or adenomatous nodules (58%) (Fig. 1), 166 hyperplastic nodules (36%), 2 infarcted nodules (<1%), 1 hyalinizing trabecular tumor (<1%), and 1 parathyroid adenoma (<1%). The remaining 21 cases (5%) demonstrated LT only without a dominant nodule documented, although 116 cases overall (25%) had histologic LT.

### *Malignant Nodules*

The mean age of the patients with malignant nodules was 55 years (range, 15-87 years), with 94 females (78%) and 27 males (22%). The preceding FNA diagnosis was benign in 2 cases (2%), AUS in 21 cases (17%), HUR in 95 cases (79%), SUS in 2 cases (2%), and malignant in 1 case (1%). Compared with benign nodules, malignant nodules were more likely to have been diagnosed as HUR on FNA ($P < .01$) (Table 2). The overall risk of malignancy (ROM) for HUR was 27% (95 of 355 cases), whereas the ROM for AUS was 10% (21 of 210 cases).

The mean size of the nodules was 2.8 cm on both ultrasound and surgical resection. Sonographic and histopathologic sizes were significantly different between malignant and benign nodules ($P < .01$ for both). Of the malignant nodules, 65 were follicular carcinomas (including Hürthle cell carcinomas) (54%), 47 were PTC (39%), 6 were poorly differentiated thyroid carcinomas (5%) (Fig. 2), 2 were medullary carcinomas (2%), and 1 was an

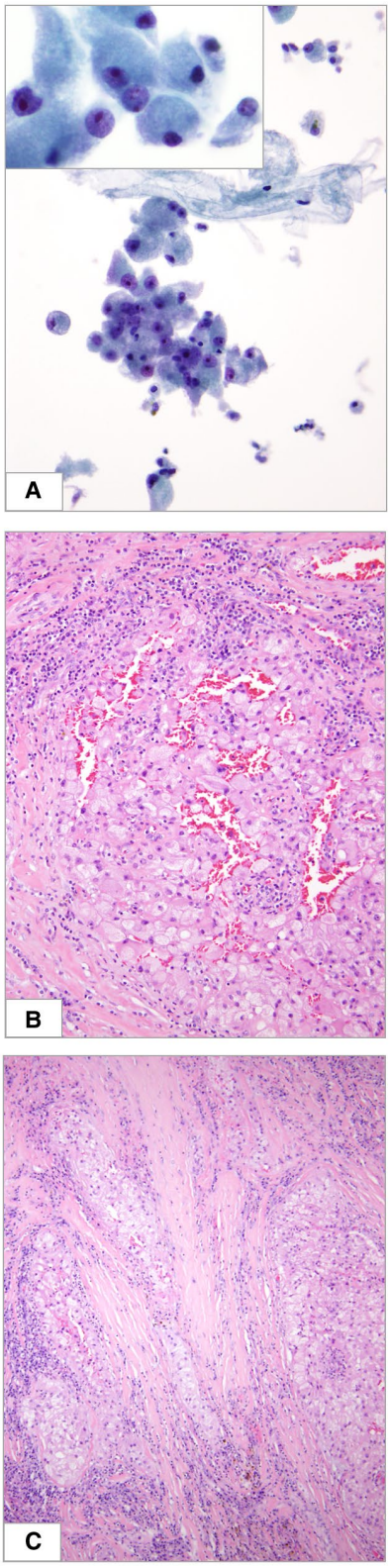


**Figure 2.** Example of a malignant nodule in the current study cohort. (A) The fine-needle aspiration specimen was composed of cells with abundant oncocytic cytoplasm, round nuclei, and prominent nucleoli. (B and C) The subsequent surgical resection specimen demonstrated a widely invasive, poorly differentiated thyroid carcinoma.

undifferentiated carcinoma (1%). Of the 47 PTC cases, 24 were the follicular variant of PTC (20%), 16 were non-follicular variants (including classic, oncocytic, and solid variants) (13%), and 7 did not have a subtype specified (PTC, NOS) (6%). Twenty-two cases (18%) demonstrated histologic LT. Multiple nodules were detected in 74 cases overall (61%). These included 55 of 81 nodules for which ultrasound evaluation was available (68%) and 19 of 40 nodules that were evaluated macroscopically (48%). Among the entire cohort, there was not a statistically significant difference noted with regard to the malignancy rate regardless of the presence or absence of LT, although there was a weak statistical trend ($P = .12$). The malignancy rate also did not differ within the setting of solitary or multiple nodules ($P = .52$) or when considering concurrent multinodularity and LT ($P = .77$).

## DISCUSSION

Hürthle cell metaplasia is common in thyroid nodules and can be observed in both malignant and benign thyroid disease, including nonneoplastic conditions such as LT or multinodular hyperplasia. For this reason, the evaluation of HC FNA can be challenging, especially given the lack of specificity of morphologic features in identifying neoplasia or differentiating benign from malignant nodules in cytologic preparations. To aid in this differential, TBSRTC has recommended that clinical features can be useful in the evaluation of HC FNA. In particular, TBSRTC has offered that it is acceptable to diagnosis HC FNA as AUS/FLUS rather than HUR in a patient with multiple thyroid nodules or LT.[10]

In the current multi-institutional study, a large cohort of HC FNA specimens was evaluated to determine whether this approach suggested by TBSRTC is justified. Overall, we found that 79% of the 576 resected Hürthle cell–predominant nodules were benign, whereas the remaining 21% were malignant. More specifically, the ROM for the HC FNA specimens diagnosed as HUR was 27%, whereas that of specimens diagnosed as AUS was 10%. The ROMs for AUS with a predominance of Hürthle cells (AUS-HC) and HUR have been highly variable in the literature, with rates ranging from 0% to 26% for AUS-HC[11-16] and from 14% to 45% for HUR.[2,6,7,15,17-28] However, the median ROMs for AUS-HC and HUR among these studies were 11% and 23%, respectively, similar to the findings we observed in the cohort in the current study. Our study did not specifically address the underlying rationale for

classifying thyroid aspirates as AUS-HC rather than HUR. The findings indicated that the number of nodules present should not determine this distinction; however, other parameters such as overall cellularity, abundance of colloid, and cell cohesiveness undoubtedly factor into the classification of Hürthle cell nodules and are able to stratify such lesions to a limited extent.

Among benign nodules, we found that the incidence of multinodularity was 64% compared with 61% in malignant nodules ($P = .52$). To the best of our knowledge, prior studies evaluating the significance of multinodularity in HC FNA specimens have been limited. However, one study by Turanli et al did not find a statistically significant difference in multinodularity in benign (53%) versus malignant (43%) nodules.[29] Another study by Sclabas et al evaluated multinodularity within the setting of all indeterminate FNA specimens, in which again no difference was found with regard to malignant nodules.[22] In the histologic evaluation of follicular neoplasms, including both Hürthle cell and non–Hürthle cell lesions, the number of nodules has been associated with ROM.[23] However, among all thyroid nodules, the significance of multinodularity on ROM has been highly variable in the literature. In a meta-analysis of 14 studies, a slightly lower ROM was noted within the setting of multinodular goiter, although this difference only was observed when including studies outside of the United States from iodine-deficient areas.[30] Although we found no overall difference in ROM between Hürthle cell nodules in solitary or multinodular thyroids, all 10 patients in the current study cohort who had >1 nodule with a preceding HC FNA specimen were found to have benign findings on surgical resection. This finding in a limited number of cases did not reach the level of statistical significance, but at least raises the possibility that an AUS-HC diagnosis may be warranted in the case of a patient with multiple Hürthle cell–rich nodules (vs multiple non–Hürthle cell or just radiographically detected nodules). However, a caveat to this possibility is that there potentially could be sampling of "multiple" nodules, which in fact are different areas of a single large and/or irregular lesion or a multifocal tumor. Although close radiologic correlation may help with this distinction, in some cases the distinction may not always be possible. A larger series of such cases is needed to examine this specific uncommon scenario further.

In addition, in the current study, we also evaluated the rate of histologic LT among benign nodules (25%) compared with malignant nodules (18%), although the difference we observed did not reach statistical significance ($P = .12$). This finding is similar to those of prior studies, which also did not find a difference in the rate of LT among benign and malignant nodules with a preceding HC FNA specimen.[19,31] In the study by Canberk et al, histologic LT was identified in 53 of 213 thyroids with benign nodules (25%) and in 14 of 56 malignant thyroids (25%).[31] Roh et al, who included both clinical, radiologic, and histologic criteria for Hashimoto thyroiditis, also did not find a statistical difference with regard to the ROM among nodules with a preceding HUR FNA specimen (25.2 vs 9.5%; $P = .081$).[19] However, given that the ROM for cases without Hashimoto thyroiditis more closely approached the expected ROM for AUS/FLUS,[10] the authors suggested that it may be more appropriate to diagnose these HC FNA cases as AUS/FLUS rather than HUR.[19] When using only cytologic findings in HC FNA specimens that are suggestive of LT (ie, with markedly increased lymphocytes), there also have been variable results reported in the prediction of ROM for HC FNA specimens.[2,9] Although not the primary focus of the current study, the data presented herein reinforced the idea that the impact of LT on the ROM for Hürthle cell–rich aspirates is limited, demonstrating only a weak statistical trend that did not rise to the level of statistical significance in multiple studies. Nevertheless, even a minimal impact on ROM within the setting of LT is consistent with favoring an AUS diagnosis over HUR within this context.

Limitations of the current study included variability in the assessment of multinodularity. Although the majority of cases had imaging results available, a subset relied on macroscopic pathologic examination, and it was unclear whether the latter would have had clinically or radiologically detectable multinodularity at the time of FNA. Limitations in data availability also prohibited further assessment of more granular findings, such as the number and size of additional thyroid nodules. In addition, because our criterion for LT included only histologic examination, the results of the current study may not have captured cases with reporting bias (ie, LT present but not documented in the surgical pathology report). In addition, histologic LT can be a somewhat nonspecific finding and is, of course, only known after surgical resection is performed. The inclusion instead of patients with true autoimmune thyroiditis or convincing radiologic

evidence of thyroiditis may be more clinically relevant. However, limited access to detailed information in the patient medical records served as a barrier to providing a more complete characterization of these patients. Finally, given that there was not a central review of cytology slides, there likely was some variability in the criteria for FNA diagnosis between institutions as well as individual cytopathologists. Subjectivity with regard to what constitutes a predominance of Hürthle cells beyond what is acceptable for benign/reactive conditions could have affected the AUS threshold and overall case selection. However, pooling of the data from all institutions may have minimized any potential biases in diagnostic criteria.

The results of the current study demonstrated that multinodularity and LT were not significantly different in benign and malignant Hürthle cell–predominant nodules (including cases that currently are classified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features, which still require surgical resection). The large, multi-institutional data set in the current study suggests that the option in TBSRTC for downgrading HC FNA specimens from HUR to AUS solely on the basis of multinodularity generally is unwarranted. The specific scenario of multiple Hürthle cell nodules may represent an exceptional circumstance warranting further study along with other factors contributing to risk stratification among Hürthle cell–rich thyroid aspirates.

## FUNDING SUPPORT

No specific funding was disclosed.

## CONFLICT OF INTEREST DISCLOSURES

Vickie Y. Jo reports that her spouse received a salary from Merck and Company for work performed outside of the current study. The other authors made no disclosures.

## AUTHOR CONTRIBUTIONS

**Kristine S. Wong:** Data curation, formal analysis, investigation, methodology, writing–original draft, and writing–review and editing. **Vickie Y. Jo:** Data curation, formal analysis, investigation, methodology, and writing–review and editing. **Alarice C. Lowe:** Data curation, investigation, and writing–review and editing. **William C. Faquin:** Data curation, investigation, and writing–review and editing. **Andrew A. Renshaw:** Data curation, investigation, and writing–review and editing. **Akeesha A. Shah:** Data curation, investigation, and writing–review and editing. **Michael H. Roh:** Data curation, investigation, and writing–review and editing. **Edward B. Stelow:** Data curation, investigation, and writing–review and editing. **Jeffrey F. Krane:** Conceptualization, methodology, project administration, supervision, and writing–review and editing.

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