Bethesda Categorization of Thyroid Nodule Cytology and Prediction of Thyroid Cancer Type and Prognosis

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Background: Since its inception, the Bethesda System for Reporting Thyroid Cytopathology (TBS) has been widely adopted. Each category conveys a risk of malignancy and recommended next steps, though it is unclear if each category also predicts the type and extent of malignancy. If so, this would greatly expand the utility of the TBS by providing prognostic information in addition to baseline cancer risk.

Methods: All patients prospectively enrolled into the authors' thyroid nodule database from 1995 to 2013 with histologically proven malignancy were analyzed. The primary ultrasound-guided fine-needle aspiration cytology (AUS, atypia of unknown significance; FN, follicular neoplasm; SUSP, suspicious; M, malignant) was correlated with the type of thyroid cancer and histological features known to impact prognosis and recurrence, including lymph node metastasis (LNM), lymphovascular invasion, and extrathyroidal extension (ETE). Primary cytology was separately correlated with higher risk malignancy.

Results: A total of 1291 malignancies were identified, with primary cytology AUS in 130 cases, FN in 241 cases, SUSP in 411 cases, and M in 509 cases. AUS, SUSP, and M cytology were progressively associated with an increasing risk of high-risk disease ($p < 0.001$), LNM ($p < 0.001$), ETE ($p < 0.001$), and margin positivity ($p < 0.001$). Notably, 71% of malignancies with AUS cytology were follicular variants of papillary thyroid cancer compared with 63% with SUSP cytology and only 20% with M cytology. In contrast, high-risk malignancies were diagnosed in only 4% with AUS cytology, but 9% and 27% with SUSP and M cytology, respectively. FN conveyed a significantly increased risk of follicular thyroid carcinoma compared with all other types (28% vs. 2%; $p < 0.001$). A composite endpoint of recurrence, distant metastases, and death similarly increased as cytology progressed from AUS to SUSP to M ($p < 0.001$).

Conclusion: In addition to predicting cancer prevalence, the TBS also imparts important prognostic information about cancer type, variant, and risk of recurrence. These data extend the utility of TBS classification by fostering an improved understanding of the risk posed by any confirmed malignancy.

Introduction

THYROID NODULES ARE INCREASINGLY common and require evaluation to rule out malignancy. Cytologic analysis of fine-needle aspiration (FNA) material is the primary modality for initial evaluation (1–4). In 2007, the National Cancer Institute convened a state of the science conference with the goal of defining consistent thyroid cytology terminology that also conveyed malignancy risk. From this, the Bethesda System for Reporting Thyroid Cytopathology (TBS) was developed, and has since been widely adopted (5).

In most clinical settings, nodule cytology is now classified into one of six Bethesda categories. Benign cytology is the most common result, and accurately predicts a benign nodule. Three cytologically indeterminate groups imply an adequate yet morphologically abnormal sample in which the risk of malignancy is increased though not confirmed. Such samples are classified as atypia (or follicular lesion) of undetermined significance (AUS), suspicious for a follicular neoplasm (FN), or suspicious for malignancy (SUSP), and convey a 5–15%, 15–30%, and 60–75% risk of malignancy, respectively (5). Malignant (M) cytology conveys a highly

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predictive 97–99% risk of cancer, and thyroidectomy is generally indicated. Such estimates have led to improved (6), albeit still imperfect, preoperative risk assessment. This in turn has fostered standardized care recommendations based upon published evidence (7–10).

Nonetheless, the histopathologic interpretation of resected thyroid tissue remains the gold standard for diagnosis. Beyond simply confirming benign or malignant disease, histopathologic characterization also provides important prognostic information predicting future risk of recurrence and death. For example, histologic variants of papillary thyroid carcinoma (PTC) are now routinely identified, as some (such as tall-cell variant PTC) are more aggressive and predisposed to recurrence. Similar associations exist when extrathyroidal extension (ETE) or lymph node metastasis (LNM) are confirmed. While prognostic information has long been gleaned from histopathology assessment, such information would be of even greater value if some or all such prognostic information was available preoperatively (5).

To date, pilot data have suggested that Bethesda categorization may indeed be able to provide more than just cancer risk assessment (11,12) and possibly inform the preoperative likelihood of low- versus high-risk cancer phenotypes. Furthermore, such data also suggest that Bethesda classification may predict high-risk histologic features such as LNM, ETE, or lymphovascular invasion (LVI). However, further data are needed to validate such findings. Importantly, in 1995, the authors' cytology department implemented a classification system identical (13) to that adopted by the Bethesda consensus. Separately, a prospective research database has been maintained of all patients seeking evaluation of a clinically relevant thyroid nodule throughout the authors' healthcare system. Together, these data have provided the means to perform a large-scale investigation of the prognostic power of TBS effectively. It was hypothesized that TBS may inform more than just the associated prevalence (or risk) of thyroid malignancy, and may also provide improved determination of the type of malignancy, measures of disease aggressiveness, and, ultimately, prognosis.

Methods

All patients prospectively evaluated in our thyroid nodule longitudinal cohort study at the Brigham & Women's Hospital (BWH) between 1995 and 2013 were analyzed. All patients were evaluated for a thyroid nodule >1 cm in maximal diameter. From this cohort, all patients with histologically confirmed malignancy were identified, and these records were correlated with their preoperative FNA cytology. This analysis was confined to that of nodules with initial indeterminate (AUS, FN, SUSP) or M cytology, as such cases identify >97% of malignancies in the cohort (13). For each case, the type of cancer, discrete histopathologic features, and other prognostic variables were obtained. These data were then compared between the four groups with AUS, FN, SUSP, or M cytology.

Briefly, ultrasound (US) evaluation was performed by one of four radiologists with expertise in thyroid evaluation, using a 6–15 MHz transducer (GE Logic 9; GE Healthcare, Milwaukee, WI). The length, width, and depth of each nodule were documented, in addition to each nodule's solid or cystic content, as previously described (13–21). FNA was performed

by one of four thyroidologists under direct US guidance. A 25-gauge needle was typically used to obtain three samples per nodule, and FNA cytology was evaluated by BWH cytopathologists. While many cases in this study predate the publication of the TBS (22), all BWH cytopathologists had been using identical terminology (implying identical meaning) since 1995 (13). This allowed the utility of TBS to be investigated over two decades.

All cytology was classified into one of six categories identical to the Bethesda system, with an associated risk of malignancy: non-diagnostic, benign (0–3% risk), AUS (5–15% risk), FN (15–30% risk), SUSP (60–75% risk), or M (97–99% risk). For patients with multiple nodules in the same gland, data were classified and analyzed according to the highest risk TBS obtained for the patient, as this was most likely to inform clinical decision making in the real-world context.

Each cancer was classified according to the American Joint Committee on Cancer (AJCC) criteria (23). For PTC, subtype variants were documented such as the tall-cell variant, follicular variant, classical variant, diffuse sclerosing variant, Warthin-like variant, and others, as listed in Supplementary Tables S1 and S2 (Supplementary Data are available online at www.liebertpub.com/thy). In rare cases, where two or more histologic variants of PTC were identified in the same gland, each patient was classified using the highest risk variant identified, as this would again be most likely to inform clinical decision making.

Independent of other pathologic features, all cancers were classified as lower-, intermediate-, or higher-risk disease (Supplementary Table S1) in order to allow comparison among cohorts with differing initial FNA cytology. Separately, each cancer was assessed for the presence of local LNM, LVI, ETE, and documentation of a positive microscopic tumor margin. Cancers were also documented as either unifocal or multifocal. Finally, thyroid cancer-specific mortality, as well as the absence or presence of distant metastatic disease, was documented (16,17).

Quantitative data are shown as mean $\pm$ standard deviation (*SD*), compared using one-way analysis of variance, whereas numbers and percentage are provided for qualitative data. Percentages were compared using the chi-square test. Logistic regression analyses were used to study the associations between the TBS and the risk of lower-, intermediate-, and higher-risk cancer and pathological behavior of cancer, including LNM, ETE, and margin positivity. All analyses were additionally corrected for confounders, including age, sex, nodule size, and nodule component. All tests were two-sided, and a *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS for Windows v13.0 (SPSS, Inc., Chicago, IL).

This protocol was approved by the Investigational Review Board at BWH.

Results

From 1995 to 2013, a prospective cohort analysis was performed of 1291 patients with AUS, FN, SUSP, or M FNA cytology who underwent thyroidectomy and were diagnosed with thyroid cancer. Demographic and nodule details are shown in Table 1. Seventy-nine percent of this cohort was female, and the mean patient age was 48.0 ± 14.9 years. Most

TABLE 1. BASELINE PATIENT AND NODULE CHARACTERISTICS

	<i>All patients</i>	<i>Primary cytology diagnosis</i>			
		<i>AUS</i>	<i>FN</i>	<i>SUSP</i>	<i>M</i>
<i>n</i>	1291	130	241	411	509
Age (years)	48 ± 15	50 ± 14	50 ± 16	48 ± 15	47 ± 15
Sex (% female)	1022 (79%)	96 (74%)	193 (80%)	335 (82%)	398 (78%)
Nodule size (mm)	24 ± 14	25 ± 14	27 ± 15	24 ± 12	22 ± 14
Nodule content					
Solid	817 (63%)	68 (52%)	169 (70%)	234 (57%)	346 (68%)
<25–50% cystic	451 (35%)	56 (43%)	70 (29%)	171 (42%)	154 (30%)
>75% cystic	23 (2%)	6 (5%)	2 (1%)	6 (1%)	9 (2%)

AUS, atypia of undetermined significance; FN, follicular neoplasm; SUSP, suspicious for malignancy; M, malignant.

nodules were solid, and nodule size averaged 24 ± 14 mm. These data confirm a typical cohort presenting for nodule assessment. While the most common FNA cytology was M (*n* = 509), cytology was SUSP in 411 cases, FN in 241, and AUS in 130.

The TBS predicted the type of thyroid cancer (*p* < 0.01) as well as the presence of higher-risk malignancy (*p* < 0.001). For example, 11/14 (79%) medullary thyroid carcinomas, 8/10 (80%) anaplastic carcinomas, and 17/19 (89%) metastatic non-thyroidal malignancies were classified as M on initial FNA cytology. Similarly, the tall-cell variant of PTC was identified in 12% with M FNA cytology compared with 3% with SUSP and <1% with AUS cytology (*p* < 0.001). In contrast, the follicular variant of PTC was documented in 71% of malignancies with initial AUS cytology compared with 63% with SUSP cytology and only 20% with M cytology (*p* < 0.001). These data are shown in Table 2, and together demonstrate the progressive risk of higher-risk disease as initial cytology progresses from AUS to SUSP to M.

Initial cytology FN, however, did not demonstrate the assumed increasing risk observed with AUS, SUSP, and M cytology, but rather provided unique prognostic information. Notably, 28% of malignancies with FN cytology proved to be follicular thyroid carcinomas (FTC). This compares with only 2% of FTC in all other cytologic groups (*p* < 0.001).

Furthermore, 10 high-risk FTCs were identified among all patients during 18 years, but the majority (7/10; 70%) demonstrated initial FN cytology. Separately, 11/17 (65%) poorly differentiated carcinomas presented with initial FN cytology. This compares with only four with SUSP cytology and two with M cytology (*p* < 0.001). Logistic regression confirmed that male sex (odd ratio [OR] = 2.707 [confidence interval (CI) 1.114–6.575], *p* = 0.028), age ≥ 45 years (OR = 2.599 [CI 1.009–6.695], *p* = 0.048), and solid parenchyma (OR = 3.053 [CI 1.097–8.494], *p* = 0.033) further predicted high-risk cancer in this FN cytology cohort, while nodule size did not (OR = 1.018 [CI 0.995–1.042], *p* = 0.125).

Beyond predicting the type of thyroid cancer, this study sought to determine if initial FNA cytology predicted distinct histopathologic or prognostic features of malignancy. Importantly, TBS progressing from AUS, to SUSP, to M increasingly predicted the risk of LNM (*p* < 0.001), ETE (*p* < 0.001), and a positive tumor margin (*p* < 0.001) on microscopic analysis (Table 3).

To determine if confounding variables of patient age, nodule size, or cystic component impacted differing cytologic groups, logistic regression was also performed to determine high-risk disease. Cytologically indeterminate (AUS, FN, and SUSP) groups were negatively correlated with high-risk cancer (OR = 0.264 [CI 0.192–0.363], *p* < 0.001), lymph

TABLE 2. TYPE AND VARIANTS OF THYROID CANCER WITH ASSOCIATED PREOPERATIVE CYTOLOGIC DIAGNOSIS

<i>Type of cancer</i>	<i>Primary Bethesda classification</i>				<i>p for difference</i>	<i>p for trend</i>
	<i>AUS</i> (<i>n</i> = 130)	<i>FN</i> (<i>n</i> = 241)	<i>SUSP</i> (<i>n</i> = 411)	<i>Malignant</i> (<i>n</i> = 509)		
Papillary carcinoma:						
Follicular variant	92 (71%)	93 (39%)	259 (63%)	104 (20%)	<0.001	<0.001
Classic variant	21 (16%)	46 (19%)	106 (26%)	257 (51%)	<0.001	<0.001
Tall-cell variant	1 (<1%)	5 (2%)	14 (3%)	59 (12%)	<0.001	<0.001
Other variants ^a	5 (4%)	15 (6%)	19 (5%)	42 (8%)	0.086	0.056
Follicular carcinoma:						
Minimally invasive:	11 (9%)	60 (25%)	4 (1%)	2 (<1%)	<0.001	<0.001
Aggressive variants ^a	0	7 (3%)	1 (<1%)	2 (<1%)	0.001	0.105
Poorly differentiated carcinoma	0	11 (5%)	4 (1%)	2 (<1%)	<0.001	0.025
Medullary carcinoma	0	2 (<1%)	1 (<1%)	11 (2%)	0.021	0.016
Anaplastic carcinoma	0	2 (<1%)	0	8 (2%)	0.038	0.057
Non-thyroid malignancy ^a	0	0	2 (<1%)	17 (3%)	<0.001	<0.001
Complete histology unavailable	0	0	1 (<1%)	5 (1%)	0.164	0.041

^aComplete histopathologic descriptions available in Supplementary Table S2.

TABLE 3. ASSOCIATION OF INITIAL BETHESDA CLASSIFICATION WITH LOWER-, INTERMEDIATE-, AND HIGHER-RISK THYROID CANCERS AND ADVERSE HISTOPATHOLOGIC FINDINGS

	All nodules	Primary Bethesda classification:			
		AUS	SUSP	M	FN
<i>Risk stratification:</i>					
Lower-risk cancer	548 (43%)	92 (71%)	259 (63%)	104 (21%) ^a	93 (39%)
Intermediate-risk cancer	528 (41%)	33 (25%)	116 (28%)	264 (52%) ^a	115 (48%)
Higher-risk cancer	209 (16%)	5 (4%)	35 (9%)	136 (27%) ^a	33 (14%)
<i>Histologic features:</i>					
Lymph node metastasis	201 (16%)	4 (3%)	33 (8%)	158 (31%) ^a	6 (3%)
Lymphovascular invasion	266 (21%)	8 (6%)	45 (11%)	162 (32%) ^a	51 (21%)
+ Microscopic margin	166 (13%)	9 (7%)	40 (10%)	92 (18%) ^a	25 (10%)
Extrathyroidal extension	227 (18%)	10 (8%)	36 (9%)	145 (29%) ^a	36 (15%)
Multifocality ≥1 cm	152 (12%)	16 (12%)	44 (11%)	78 (15%)	14 (6%)
Composite endpoint ^b	54 (4%)	1 (1%)	11 (3%)	36 (7%) ^a	6 (3%)

AUS, SUSP, and M cohorts demonstrate a continuum of increasing risk, while FN imparts unique attributes.

^a $p < 0.01$ for differences and trend among AUS, SUSP, and M cohorts.

^bComposite endpoint inclusive of local recurrence, distant metastases, or death.

node positivity (OR=0.127 [CI 0.088–0.184], $p < 0.001$), LVI (OR=0.323 [CI 0.243–0.428], $p < 0.001$), positive microscopic tumor margins (OR=0.458 [CI 0.327–0.642], $p < 0.001$), ETE (OR=0.288 [CI 0.213–0.391], $p < 0.001$), multifocality (OR=0.557 [CI 0.394–0.787], $p < 0.001$), and bilateral disease (OR=0.562 [CI 0.424–0.744], $p < 0.001$) when compared with the cytologically M group.

Finally, to allow easier translation of these data into clinical practice, all malignancies were categorized as lower, intermediate, or higher risk, as defined in Table 3 and Supplementary Table S1. High-risk malignancy was identified in 27% of cases when cytology was M, but only in 9% and 4% when cytology was SUSP or AUS, respectively ($p < 0.01$). Interestingly, initial cytology FN predicted modestly increased risk (14%) of high-risk malignancy compared with 4% in AUS and 9% in SUSP, likely influenced by a large proportion of poorly differentiated carcinomas and high-risk FTCs. The predictive value of initial Bethesda classification was also assessed on a composite endpoint inclusive of local recurrence, distant metastases, and death. This endpoint increased from 1%, 3%, 3%, to 7% with initial AUS, FN, SUSP, and M cytology ($p < 0.001$).

Discussion

With its inception in 2007, the Bethesda system standardized thyroid nodule cytologic terminology. In doing so, the prevalence of malignancy could be effectively translated to both the patient and the practitioner, advancing and informing care decisions. However, preoperative risk assessment remains imperfect as we seek to inform the patient not only of the chance their nodule may be cancerous, but also the type and inherent risk such a cancer may pose to overall health. The present data analyzing nearly 1300 consecutive patients over 18 years demonstrate an impressive expansion to the importance of Bethesda categorization, confirming its ability to impart prognostic information about the cancer type, histologic profile, and ultimate patient outcome. As FNA cytology progresses from AUS to SUSP to M, there exists an increasing likelihood of higher-risk thyroid cancer, high-risk variants of PTC, and adverse histologic findings.

Cytology classified as FN implies separate prognostic information, significantly increasing the risk of FTC and poorly differentiated carcinoma. Together, these data extend the utility of the TBS beyond simply an assessment of cancer likelihood by fostering improved understanding of the risk posed by such a thyroid malignancy.

FNA cytology classified as AUS has long represented the lowest risk category within the cytologically indeterminate grouping. Initial Bethesda publications suggested that the malignancy risk associated with this cytology was only 5–15% (5). Others have demonstrated that repeat aspiration can ultimately classify such lesions as benign nearly 50% of the time (13). The present data broaden the understanding of AUS cytology, further demonstrating that any potential malignancy is highly likely to be lower-risk disease, most commonly a follicular variant of PTC. Furthermore, metastatic lymphadenopathy, ETE, or other worrisome histologic features can be expected to occur in <10% of identified cancers. Such impressive low-risk disease may allow some patients with AUS cytology to consider conservative monitoring of their nodule, acknowledging that even if malignancy is identified, associated risk may be impressively low. This contrasts with nodules with SUSP or M cytology, in which higher-risk disease is much more likely.

FNA cytology classified as FN has also been considered low risk, in large part because of published data confirming only 20–30% of such lesions prove malignant. The present data modify this understanding by demonstrating a risk of higher-risk disease among this cohort exceeding that found in nodules with SUSP cytology (14% in FN vs. 9% in SUSP; $p > 0.05$). Importantly, 11/17 poorly differentiated thyroid carcinomas detected over 18 years had initial FN cytology. Furthermore, 28% of malignancies were FTC, including 70% of the highest risk (widely invasive) phenotype. Separate from AUS, SUSP, and M cytology (which appear to represent a continuum of prognostic risk), FN appears to impart unique and independent information. While hemithyroidectomy is often considered for nodules with AUS or FN cytology, these data may increase consideration for near-total thyroidectomy in select patients with FN cytology (especially when higher-risk sonographic or molecular features are present) given the increased chance of

higher-risk disease that would benefit from complete resection. However, it is important to note that surgical decisions must also consider the likelihood of malignancy, acknowledging that the proportion of FN nodules which prove malignant is lower than that in SUSP nodules. These data expand the prognostic power of a system already used by many, and, in so doing, support its widespread adoption. A similar parallel has been observed with thyroid ultrasound. While formerly ultrasound was primarily used for measurement of nodule size and cystic content, improved technology combined with formal investigation has confirmed the ability of sonographic assessment to improve preoperative cancer risk assessment. The presence of calcifications, the parenchyma appearance, and margin contour are now routinely assessed, allowing improved preoperative prediction of malignancy. Combined with molecular analysis (24,25), Bethesda cytologic classification and sonographic assessment are significantly improving individual assessment of a patient's risk and thereby guiding appropriate recommendations.

Some limitations of this study must be acknowledged. The TBS was introduced in 2007, though the study dates back to 1995. Small changes in classification and meaning may therefore have occurred over time before the TBS conference provided a national standard. However, classifications identical to the TBS have been utilized at BWH since 1995, with early publications (13) largely influencing the Bethesda conference itself. In addition, there exists high inter-observer variability when interpreting thyroid FNA cytology as well as histopathology. Although it would be ideal to have two blinded pathologists interpret all data, such a mandate is largely impractical over such a long and large study. Furthermore, these data are generated from a consecutive real-world population and thus may prove most transferrable to the clinical practice of others.

In the future, molecular analysis of thyroid nodules may provide further insight into the TBS classification. The Thyroid Cancer Gene Atlas has already provided important insight into the molecular basis of PTC (26), and separate publications have demonstrated the distribution of genetic mutations among nodules, both benign and malignant (27). However, no molecular test has yet proven superior to FNA cytology for the purposes of initial diagnostic evaluation. However, while awaiting results from future studies, it seems likely that distinct molecular signatures will correlate with specific Bethesda classifications given their above association with low- or high-risk malignancy. Further investigation should seek to determine if the prognostic utility of the TBS changes based on the use of such molecular tests.

In summary, these data extend the utility of TBS classification beyond simply an assessment of cancer likelihood by fostering an improved understanding of the risk posed by thyroid malignancy if confirmed. In addition to predicting thyroid cancer prevalence, the TBS classification should now be used by physicians to inform patients of the potential type, variant, and histologic properties, which are likely if cancer is identified. In doing so, patients and physicians are better informed, while subsequent care is improved.

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