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Features Associated with Locoregional Spread of Papillary Carcinoma Correlate with Diagnostic Category in The Bethesda System for Reporting Thyroid Cytopathology

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Abstract

Introduction—Most malignancies identified by thyroid fine needle aspiration (FNA) are papillary thyroid carcinoma (PTC). We set out to determine if clinically adverse features of PTC correlate with the preceding cytologic diagnosis.

Methods—Thyroid FNA diagnoses were correlated with subsequent histopathologic findings.

Results—From 6175 thyroid FNAs, histologic follow-up confirmed PTC in 52/184 (28%) of atypia of undetermined significance (AUS) FNAs, 52/190 (27%) suspicious for follicular neoplasm FNAs, 182/229 (79%) of suspicious for malignancy FNAs, and 188/198 (95%) of malignant (M) FNAs. Gender, age, and disease multifocality did not differ among FNA-diagnosis groups. However, PTCs following a M FNA were more likely to be higher AJCC T and N stage, have lymphovascular invasion and/or extrathyroidal extension. Two patients had distant metastasis at initial surgery, while 16 developed subsequent recurrence/ and/or metastasis; all had a preceding M FNA. High-risk histologic subtypes of PTC also stratify to the M category accounting at least partly for the association of cytologic diagnosis with adverse pathological parameters. Conversely, follicular variants of PTC predominate in non-M categories.

Conclusions—The Bethesda System for Reporting Thyroid Cytopathology conveys malignancy risk, but also predicts the presence of pathological risk factors and disease progression when the malignancy is PTC. M diagnoses identify higher risk PTCs, while AUS diagnoses identify low-risk PTCs, mostly follicular variants. These findings support the concept of conservative clinical management for some patients with AUS, while suggesting that a central neck dissection may be routinely justified in some patients with a M FNA.

Keywords

Thyroid; Thyroid nodule; Fine needle aspiration; Bethesda system; Papillary carcinoma

Introduction

The Bethesda System for Reporting Thyroid Cytopathology (TBS) provides a six-tiered diagnostic framework that uses defined criteria to promote uniformity in the reporting of

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thyroid aspirates [1]. One of the major advantages of this scheme is that the individual diagnostic categories are associated with defined risks of malignancy allowing for standardized management algorithms for each diagnosis.

As pointed out by others [2, 3], the low mortality associated with thyroid cancer means that treatment is largely directed at preventing locoregional morbidity rather than averting death. Ideally, therefore, disease detection via fine needle aspiration (FNA) would also be directed at identifying those cancers posing significant risk for locoregional spread in addition to the small subset of tumors (such as medullary, poorly differentiated, and undifferentiated carcinomas) that carry substantial risk of death.

The vast majority of malignancies identified by thyroid FNA are papillary thyroid carcinoma (PTC), a cancer with an overall excellent prognosis. Factors that have been associated with higher risk for adverse outcomes with PTC include male gender, older age (>45 years) at the time of diagnosis, large tumor size, extrathyroidal extension of tumor, and certain histologic subtypes [4, 5]. We recently noted that histologic follow-up of AUS diagnoses at our institution yielded a disproportionate number of malignancies classified as follicular variant of papillary carcinoma (FVPTC) [6], an observation also made by other investigators [7-9]. FVPTC is a controversial entity notable for the poor reproducibility of its histologic diagnosis [10, 11] as well as the indolent behavior of encapsulated variants with borderline cytologic features [12, 13] that has led some authors to suggest that a subset of FVPTC should be reclassified [14, 15]. The association of AUS with FVPTC led us to theorize that malignancies detected by AUS may largely represent borderline FVPTCs with minimal potential for malignant behavior. Moreover, we theorized that those cytologic diagnoses most associated with PTC in TBS, progressing in severity from AUS to suspicious for malignancy (SUS) and malignant (M), might correlate both with histologic subtype as well as with features of PTC associated with disease progression. If such a correlation exists, it could have implications for clinical management algorithms within TBS. To address this question, we compared surgical outcome with the preceding cytologic diagnosis for thyroid FNAs performed at our institution over a greater than five year period using TBS terminology.

Materials and Methods

Following approval by the institutional review board, a retrospective analysis was conducted of all thyroid fine needle aspirations performed at the Brigham and Women's Hospital from January 2005 through May 2010. Over this period, 6175 thyroid FNAs were performed under ultrasound guidance by staff endocrinologists, without routine on-site evaluation. Aspirates from 3-4 passes using a 25-gauge needle were collected immediately in CytoLyt® (Hologic, Inc.; Marlborough, MA) and Papanicolaou stained ThinPrep® slides were prepared using the ThinPrep 2000® (Hologic, Inc.). Cell block preparations were not routinely made, but at the discretion of the cytologist were attempted in a small percentage of cases when adequate material was present. All cases were reported by a staff cytopathologist using a six-tiered diagnostic system and criteria essentially identical to TBS as previously described [6].

Outcome data were collected for those thyroid nodules with the cytologic diagnoses posing the greatest clinical concern for PTC: malignant (M), suspicious for malignancy (SUS), atypia of undetermined significance/follicular lesion of undetermined significance (AUS), or suspicious for a follicular (or Hürthle cell) neoplasm (FOL). Data compiled from the original surgical pathology reports of resected specimens included patient gender, age, size of the targeted nodule, the histopathologic diagnosis, and for malignant cases, prognostic indicators including multifocality, lymphovascular invasion, extrathyroidal extension, the

total number of resected lymph nodes at the time of surgery along with the number of positive nodes. Pathologic subtypes of PTC were combined into three groups for analysis purposes: 1-Pure follicular variants (including macrofollicular variants), 2-Tumors with any high-risk features noted (as per the WHO classification of PTCs [16], including diffuse sclerosing, tall cell, poorly differentiated, and columnar features), and 3-Conventional risk types (predominantly classical type PTC as well as infrequent oncocytic, clear cell, unspecified, and cribriform morular variants considered to represent comparable clinical risk to classical type PTC) [16]. The TNM stage of the tumor was determined using criteria from the most current, 7th edition of the American Joint Committee on Cancer staging manual [17]. Following primary surgical resection, any tumor recurrence or distant metastasis was recorded. The cases in this series had a median of 51 months clinical follow-up after the initial thyroid FNA (range 18-83 months).

Data processing and statistics were performed using SPSS Statistics software (version 20; IBM, Armonk, NY). Categorical analysis was performed using a Chi-squared (χ^2) likelihood ratio test, while mean tumor size was analyzed using a one-way ANOVA test. A predetermined level of significance was set at a P value of 0.05. Post hoc pairwise categorical comparisons (Bonferroni test) were performed when statistical significance was observed across all categories.

Results

During this nearly 5.5 year time period, 6175 thyroid FNAs were performed, with the distribution of diagnoses rendered using TBS criteria and nomenclature provided in Table 1. From this cohort, 192 thyroid nodules were resected following a M diagnosis on FNA, 202 nodules for a SUS diagnosis on FNA, 163 nodules for a FOL diagnosis on FNA, and 168 nodules following a single or repeat diagnosis of AUS. In addition to these cases, 6 nodules were resected after an AUS and follow-up M FNA, 27 nodules resected after an AUS and follow-up SUS FNA, 27 nodules resected after an AUS and follow-up FOL FNA, 12 nodules resected after an AUS and follow-up benign FNA, and 4 nodules resected after an AUS and follow-up non-diagnostic FNA. These cases were grouped according to the worst (most severe) FNA diagnosis (either M, SUS, FOL, or AUS), giving a total of 198 M nodules, 229 SUS nodules, 190 FOL, and 184 AUS nodules.

The overall distribution of histologic outcomes for these thyroid nodules following surgery is delineated in Table 2. The small numbers of non-PTC epithelial malignancies with significant risk of progression (medullary, anaplastic, and poorly differentiated carcinomas) appear to stratify by severity of the preceding cytologic diagnosis with the exception of the FOL category accounting both for most follicular carcinomas as well as the majority of poorly differentiated carcinomas. However, PTC accounted for the majority of the malignant surgical outcomes for all four groups and comprised 90.1% (474/526) of all thyroid carcinomas. Since we were only concerned with outcomes for PTC, other malignancies were eliminated from the subsequent analyses.

The breakdown of histologic subtypes for the PTC cases is shown in Table 3. Relative to the other categories, the M category had higher proportions of high-risk and conventional subtypes while follicular variants accounted for most PTCs in the SUS, FOL, and AUS groups. The distribution of PTC subtypes showed statistically significant differences across cytologic diagnoses ($P<0.001$) with pairwise comparisons of the M group with the AUS, FOL, and SUS diagnoses also achieving statistical significance ($P<0.001$).

There were no significant differences across diagnostic categories with regard to gender or age (Table 4). The difference in mean tumor size was statistically significant ($P<0.04$) across

all categories; the only pairwise statistically significant difference in size was PTC associated with M being significantly smaller than PTC associated with FOL ($P<0.02$). Although the M group had a slightly higher proportion of multifocal disease as well as the only 2 cases with metastasis at the initial time of surgery, these differences were not statistically significant compared with the other groups. However, also as depicted in Table 4, clear differences in other pathologic features were apparent between FNA-diagnosis groups. The distribution of cases according to cytologic diagnoses for T stage, N stage, lymphovascular invasion, extrathyroidal extension, and recurrence/metastasis was statistically significant ($P<0.001$). Each of these parameters was statistically significant when comparing M to SUS, M to AUS, and M to FOL (except T stage for M to FOL). Although no statistically significant differences were noted between the AUS and SUS categories, a trend was observed with higher percentages of cases with higher T stage, lymph node metastasis, lymphovascular invasion, and extrathyroidal extension observed in the SUS category compared to AUS. All 5 T3 PTCs associated with AUS were >4 cm. Only 1 of the 5 T3 PTCs following an AUS would have been classified as T3 based on the presence of extrathyroidal extension, but this tumor also would have been categorized as T3 based on size since it exceeded 4 cm. Only 2 PTCs had distant metastasis at the time of surgery, and 16 patients later went on to develop recurrence and/or distant lymph node metastasis after surgery; all these cases had a M FNA diagnosis preceding surgery.

None of the statistically significant parameters of T stage, N stage, lymphovascular invasion, extrathyroidal extension, and recurrence/metastasis can be directly evaluated on an initial thyroid FNA; therefore, we theorized that the stratification of these parameters may in turn be dependent on the differential distribution of PTC subtypes across cytologic diagnostic categories. To assess this possibility, we stratified these parameters both by cytologic diagnosis and PTC subtype. As shown in Table 5, statistically significant differences were noted for N stage, lymphovascular invasion, and extrathyroidal extension according to one or more subtype of PTC while nearly reaching statistical significance for T stage and recurrence/metastasis, thus supporting the conclusion that the stratification of markers of aggressive behavior by FNA category is at least in part dependent on PTC subtype.

Discussion

Our findings confirm a distinct stratification of histologic subtype of PTC according to the preceding cytologic diagnosis. Almost all PTCs identified in association with AUS were FVPTC, while M FNA diagnoses encompassed most classical variants as well as aggressive variants such as tall cell and diffuse sclerosing types of PTC. Not surprisingly, the SUS category had intermediate properties, mostly comprised of FVPTC but with small numbers of high-risk variants not observed following an AUS diagnosis, while PTC associated with the FOL category is predominantly FVPTC with infrequent tumors having a poorly differentiated component. This stratification according to cytologic diagnosis is not surprising in that a significant proportion of tumors diagnosed as FVPTC have marginal nuclear features of PTC [18] that would be a logical histologic counterpart to the lesser degrees of atypia encountered in the non-M categories, most notably the mild cytologic atypia responsible for some AUS diagnoses. Perhaps more surprising is how clearly the other PTC subtypes stratify between the AUS and M categories. This implies that AUS diagnoses suggestive of PTC are mostly classified as AUS because of the inherent borderline nuclear features of PTC in the lesional cells rather than representing suboptimal sampling of PTC possessing well-developed cytologic features, as would be typical of classical variants. Those lesions with readily recognizable cytologic features of PTC, such as frequent intranuclear pseudoinclusions, will be diagnosed as M when well sampled by FNA and, as our data indicates, are more likely to be classified as SUS than AUS (or perhaps FOL) if the lesion is suboptimally represented.

The severity of the preceding cytologic diagnosis in TBS was also predictive of histologic parameters associated with more aggressive clinical behavior. Yet, the only parameter that could potentially be directly assessed by cytologic evaluation of the original lesion is the histologic subtype of the tumor. Even this parameter, however, is not routinely assessed on FNA and in most instances may only be suggested by the cytologic features of the specimen. The implication of this finding is that more definitive features of PTC indirectly predict the likelihood of encountering features associated with more worrisome clinical behavior, such as extrathyroidal extension, despite the fact that these parameters cannot be directly assessed cytologically. Our data further indicate that the M category is particularly sensitive for detecting more commonly encountered high-risk subtypes of PTC, such as the tall cell type. This stratification of subtype within TBS framework in turn accounts at least in part for the ability of TBS classification to stratify risk for other parameters associated with more aggressive behavior.

Greater degrees of atypia detected within TBS have been known to predict the risk of malignancy within TBS framework. In fact, this risk stratification is one of the major benefits of using TBS. Our findings indicate that the severity of the diagnosis within TBS also predicts risk for locoregional complications with PTC. These observations further validate the current definitions of individual categories in TBS as well as the concept of having differing management for each diagnostic category. More significantly, if verified by others, these findings could potentially alter currently recommended clinical management algorithms. Current American Thyroid Association guidelines state that “prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)” [19]. In patients with a M FNA diagnosis in our study, lymph node metastases were encountered in 45% (64/142) of patients having any lymph nodes removed at the time of surgery, but were infrequently observed following a SUS diagnosis and present in only single cases in the AUS or FOL categories. Consequently, our findings indicate that consideration should be given to routine central compartment lymph node sampling in patients with a preceding M FNA diagnosis.

The potential clinical implications of our data for management of patients with an AUS diagnosis are intriguing. Our previously published data as well as that of some other investigators [7, 20, 21] have indicated that the overall risk of malignancy associated with the AUS diagnosis may be higher than the 5-15% rate that had been anticipated by TBS. A higher malignancy rate potentially argues for earlier surgical intervention rather than TBS recommended approach of repeating the FNA after an initial AUS diagnosis. The data in the present study, however, indicate that the low clinical risk of locoregional spread associated with the indolent malignancies detected by AUS justifies consideration of both short-term and long-term non-surgical management in appropriately selected patients within the AUS group. Of the five T3 PTCs identified in our study only one exhibited extrathyroidal extension, and all could be identified pre-operatively based on their large size. Thus, consideration should be given to stratifying management of an initial AUS based on size (as well as other potentially worrisome clinical and/or radiologic parameters) [19]. One potential approach would be to send patients with larger nodules (at least those in the T3 size range exceeding 4 cm) to surgery after a single AUS diagnosis, while initially managing patients with smaller nodules with repeat FNA. Serial ultrasound examination, possibly accompanied by repeat FNA, could represent a viable long-term management option for patients with small nodules lacking worrisome clinical or ultrasound properties. Surgery would be reserved for those individuals whose nodules progress in size, develop other concerning clinical/ultrasound features, or progress in the severity of any repeat FNA cytologic diagnosis. Because of the likely indolent behavior of such PTCs, an approach of “watchful waiting” would pose minimal risk should later surgical intervention prove

necessary. At the same time, the major risks of thyroid surgery, including vocal cord paralysis and hypocalcemia, the need for lifetime thyroid hormone replacement therapy, and the potential stigma and anxiety associated with a diagnosis of cancer would be avoided in a significant subset of patients.

The difficulty in diagnosing the FVPTC both cytologically and histologically remains a vexing problem. We had previously observed that malignancies detected in our laboratory following an AUS FNA diagnosis are largely FVPTCs [6]. Other authors have made similar observations [7-9] and descriptions of FVPTC preceding implementation of TBS have also noted that FVPTCs are often not definitively malignant on FNA [22, 23]. Histologically, the diagnosis of FVPTC is known to be notoriously poorly reproducible [10, 11]. Some authors have argued that lesions with borderline histological features of FVPTC should be reclassified into existing diagnostic categories, such as follicular adenoma, or alternative nomenclature should be adopted that sets these lesions apart from uniformly recognizable PTCs [14, 15]. These proposals have not been widely accepted to date.

Since FVPTC constitutes a larger percentage of malignancies identified with lesser degrees of cytologic atypia on FNA, the corresponding malignancy rates identified for AUS (and to a lesser degree the FOL and SUS categories) would be expected to show greater fluctuations amongst laboratories in accordance with local practice regarding the histologic threshold for diagnosing FVPTC. The consequences of such variations in practice regarding classification of FVPTC will not be readily identified since clinical outcome will be almost uniformly excellent. Nevertheless, rare instances have been reported where seemingly banal FVPTC behaved aggressive clinically [24]. Such rare cases along with medicolegal concerns make it easier to overdiagnose and overtreat patients than to manage them conservatively [18, 25]. Mindful that other categories in TBS will account for those malignancies associated with significant mortality as well as those PTCs associated with locoregional morbidity (as shown in our study), overtreatment of the low-risk lesions commonly associated with the AUS diagnosis should be avoided.

Some laboratories have reported notably low rates of AUS as well as low AUS:M ratios [2, 21, 26, 27]. These low rates may be achieved at the expense of diagnostic sensitivity [28]. Laboratories that practice in this fashion may be avoiding the potential overtreatment of AUS by simply avoiding the diagnosis altogether. This approach may have merit since lesions that could be theoretically missed are unlikely to prove harmful to the patient at least in the short-term. Whether greater sensitivity to low-risk lesions is beneficial to long-term outcome by intervening in disease progression to more aggressive (poorly differentiated or anaplastic) carcinomas is unclear, but is unlikely to be significant in most instances. Nevertheless, it will prove difficult for many cytopathologists to feel comfortable calling the subtle cytologic features associated with these lesions benign rather than AUS unless the histologic practice of diagnosing encapsulated follicular lesions with borderline cytologic features as FVPTC is significantly altered.

Our data demonstrate similar properties for PTCs detected by either the FOL or AUS diagnoses, while the FOL category additionally accounts for most follicular carcinomas detected by FNA. Nevertheless, in our population, a FOL diagnosis was almost twice as likely to result in a histologic diagnosis of PTC as follicular carcinoma. As was the case with the AUS category, we observed a malignancy rate (44.2%; 84/190) higher for the FOL category than anticipated by TBS. Also, as with AUS, however, this increased malignancy rate is largely accounted for by the presence of low-risk FVPTCs. While the overall higher rates of malignancy for AUS and FOL could argue for more aggressive management than recommended by TBS, the clinically indolent behavior of this large subset of tumors

detected with both AUS and FOL diagnoses justifies the more conservative management approach advocated by TBS.

Ideally, molecular testing would provide guidance as to which indeterminate lesions might represent malignancies with the potential for significant clinical risk and this is an area of intensive research interest at present [29-31]. As the FVPTC is currently defined, such lesions are more likely to be associated with RAS mutations, while the BRAF V600E mutation is more frequently identified with PTCs with more aggressive clinical behavior [32]. If the goal of molecular testing is to detect aggressive tumors rather than maximizing sensitivity for malignancy, then testing for BRAF V600E rather than a panel of markers also including RAS, RET/PTC, and PAX8/PPARγ may be desirable. Here, too, a consensus has not yet been achieved as to how to best use ancillary molecular testing data for indeterminate thyroid FNA specimens.

In conclusion, we have shown that the diagnostic categories in TBS for reporting thyroid cytopathology (particularly the M category) not only stratify risk of malignancy, but also correlate with the subtype of PTC as well as the presence of adverse histopathologic features. These findings may have implications for refining clinical management algorithms for patients with AUS or M diagnoses on FNA.

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References

1. Ali, SZ.; Cibas, ES. The Bethesda System for Reporting Thyroid Cytopathology. New York, NY: Springer; 2010.
2. Abele JS, Levine RA. Diagnostic criteria and risk-adapted approach to indeterminate thyroid cytodiagnosis. Cancer Cytopathol. 2010; 118:415–422. [PubMed: 21154916]
3. Henry M. The potential for overuse of atypical thyroid diagnoses. Cancer Cytopathol. 2011 Sep 16. Epub ahead of print. 10.1002/cncy.20191
4. Lang BH, Lo CY, Chan WF, et al. Prognostic factors in papillary and follicular thyroid carcinoma: their implications for cancer staging. Ann Surg Oncol. 2007; 14:730–738. [PubMed: 17103065]
5. Simpson WJ, McKinney SE, Carruthers JS, et al. Papillary and follicular thyroid cancer. Prognostic factors in 1,578 patients. Am J Med. 1987; 83:479–488. [PubMed: 3661584]
6. VanderLaan PA, Marqusee E, Krane JF. Usefulness of Diagnostic Qualifiers for Thyroid Fine-Needle Aspirations with Atypia of Undetermined Significance. Am J Clin Pathol. 2011; 136:572–577. [PubMed: 21917679]
7. Faquin WC, Baloch ZW. Fine-needle aspiration of follicular patterned lesions of the thyroid: diagnosis, management, and follow-up according to National Cancer Institute (NCI) recommendations. Diagn Cytopathol. 2010; 38:731–739. [PubMed: 20049964]
8. Layfield LJ, Morton MJ, Cramer HM, et al. Implications of the proposed thyroid fine-needle aspiration category of “follicular lesion of undetermined significance”: a five-year multi-institutional analysis. Diagn Cytopathol. 2009; 37:710–714. [PubMed: 19373907]
9. Horne MJ, Chhieng DC, Theoharis C, et al. Thyroid Follicular Lesion of Undetermined Significance: Evaluation of the Risk of Malignancy Using the Two-Tier Sub-Classification. Diagn Cytopathol. 2011 in press.
10. Elsheikh TM, Asa SL, Chan JK, et al. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. Am J Clin Pathol. 2008; 130:736–744. [PubMed: 18854266]

11. Lloyd RV, Erickson LA, Casey MB, et al. Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. Am J Surg Pathol. 2004; 28:1336–1340. [PubMed: 15371949]
12. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer. 2006; 107:1255–1264. [PubMed: 16900519]
13. Piana S, Frasoldati A, Di Felice E, et al. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. Am J Surg Pathol. 2010; 34:868–872. [PubMed: 20463572]
14. Vickery AL Jr. Thyroid papillary carcinoma. Pathological and philosophical controversies. Am J Surg Pathol. 1983; 7:797–807. [PubMed: 6660352]
15. Williams ED, Abrosimov A, Bogdanova T, Ilo M, Rosai J, Sidorov Y, Thomas GA. On behalf of the Chernobyl Pathologists Group. Guest Editorial: Two Proposals Regarding the Terminology of Thyroid Tumors. Int J Surg Pathol. 2000; 8:181–183. [PubMed: 11493987]
16. DeLellis, RA.; Lloyd, RV.; Heitz, PU., et al. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Endocrine Organs. Lyon, France: IARC Press; 2004.
17. Edge, SE.; Byrd, DR.; Compton, CC., et al. AJCC Cancer Staging Manual. 7. New York, NY: Springer; 2009.
18. Renshaw AA, Gould EW. Why there is the tendency to “overdiagnose” the follicular variant of papillary thyroid carcinoma. Am J Clin Pathol. 2002; 117:19–21. [PubMed: 11789725]
19. Cooper DS, Doherty GM, Haugen BR, et al.American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19:1167–1214. [PubMed: 19860577]
20. VanderLaan PA, Marqusee E, Krane JF. Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: Should repeat FNA be the preferred initial approach? Am J Clin Pathol. 2011; 135:770–775. [PubMed: 21502433]
21. Theoharis CG, Schofield KM, Hammers L, et al. The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution. Thyroid. 2009; 19:1215–1223. [PubMed: 19888859]
22. Logani S, Gupta PK, LiVolsi VA, et al. Thyroid nodules with FNA cytology suspicious for follicular variant of papillary thyroid carcinoma: follow-up and management. Diagn Cytopathol. 2000; 23:380–385. [PubMed: 11074641]
23. Jain M, Khan A, Patwardhan N, et al. Follicular variant of papillary thyroid carcinoma: a comparative study of histopathologic features and cytology results in 141 patients. Endocr Pract. 2001; 7:79–84. [PubMed: 11421549]
24. Baloch ZW, LiVolsi VA. Encapsulated follicular variant of papillary thyroid carcinoma with bone metastases. Mod Pathol. 2000; 13:861–865. [PubMed: 10955452]
25. Chan JK. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. Am J Clin Pathol. 2002; 117:16–18. [PubMed: 11791591]
26. Jo VY, Stelow EB, Dustin SM, et al. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol. 2010; 134:450–456. [PubMed: 20716802]
27. Krane JF, Vanderlaan PA, Faquin WC, et al. The atypia of undetermined significance/follicular lesion of undetermined significance: Malignant ratio: A Proposed Performance Measure for Reporting in The Bethesda System for Thyroid Cytopathology. Cancer Cytopathol. 2011 Sep 14. Epub ahead of print. 10.1002/cncy.20192
28. Renshaw AA. Subclassification of atypical cells of undetermined significance in direct smears of fine-needle aspirations of the thyroid: Distinct patterns and associated risk of malignancy. Cancer Cytopathol. 2011; 119:322–327. [PubMed: 21442771]
29. Ohori NP, Nikiforova MN, Schoedel KE, et al. Contribution of molecular testing to thyroid fine-needle aspiration cytology of “follicular lesion of undetermined significance/atypia of undetermined significance”. Cancer Cytopathol. 2010; 118:17–23. [PubMed: 20099311]

30. Nikiforov YE. Molecular analysis of thyroid tumors. Mod Pathol. 2011; 24:S34–S43. [PubMed: 21455199]

31. Hassell LA, Gillies EM, Dunn ST. Cytologic and molecular diagnosis of thyroid cancers. Is it time for routine reflex testing? Cancer Cytopathol. 2011 Aug 31. Epub ahead of print. 10.1002/cncy.20186

32. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab. 2003; 88:5399–5404. [PubMed: 14602780]

Table 1

Distribution of Thyroid FNA Diagnoses between 1/1/2005 and 5/31/2010

FNA Diagnosis	No. (%)
Nondiagnostic	795 (12.9)
Benign	3876 (62.8)
Atypia of Undetermined Significance	692 (11.2)
Suspicious for Follicular/ Hürthle Cell Neoplasm	242 (3.9)
Suspicious for Malignancy	260 (4.2)
Malignant	305 (4.9)
Neoplastic cells present	5 (0.1)
Total	6175 (100)

Values expressed as number with percent of total following in parentheses.

Table 2

Histologic outcome based on worst preceding FNA diagnosis.

	Malignant	Suspicious for malignancy	Follicular Neoplasm	AUS	Total
PTC	188 (94.9)	182 (79.5)	52 (27.4)	52 (28.3)	474 (59.2)
FTC	0 (0.0)	2 (0.9)	27 (14.2)	8 (4.3)	37 (4.6)
MTC	6 (3.0)	0 (0.0)	1 (0.5)	0 (0.0)	7 (0.9)
PDCar	1 (0.5)	2 (0.9)	4 (2.1)	0 (0.0)	7 (0.9)
ANA	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Benign	2 (1.0)	40 (17.5)	104 (54.7)	123 (66.8)	269 (33.6)
FNUMP	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)
HTT	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Lymphoma	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.5)	3 (0.4)
Total	**198 (100)**	**229 (100)**	**190 (100)**	**184 (100)**	**801 (100)**

Values expressed as number with percent of total following in parentheses. PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, MTC: medullary thyroid carcinoma, PDCar: poorly differentiated carcinoma, ANA: anaplastic/undifferentiated thyroid carcinoma, FNUMP: Follicular neoplasm of uncertain malignant potential, HTT: hyalinizing trabecular tumor.

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Table 3

Papillary thyroid carcinoma subtype based on worst preceding FNA diagnosis.

	Malignant	Suspicious for malignancy	Follicular Neoplasm	AUS
FV	46 (24.5)	136 (81.3)	38 (73.1)	44 (84.6)
CV	81 (43.1)	28 (13.2)	12 (23.1)	8 (15.4)
High-risk	61 (32.4) *	18 (5.5) ^	2 (3.8) #	0 (0.0)
Total	**188 (100)**	**182 (100)**	**52 (100)**	**52 (100)**

Abbreviations: FV: Follicular variant; CV: Conventional variant; AUS: Atypia of undetermined significance; FOL: Suspicious for a follicular neoplasm; SUS: Suspicious for malignancy; M: Malignant

Values expressed as number with percent of total following in parentheses.

* 24 diffuse sclerosing, 26 tall cell, and 11 with mixed diffuse sclerosing and tall cell variant/features

^ 10 diffuse sclerosing and 6 tall cell variant/features; 2 with focal poorly differentiated areas

2 follicular variants with poorly differentiated areas

P>0.001; Post hoc pairwise comparisons:
AUS v M: P<0.001
SUS v M: P<0.001
FOL v M: P<0.001
All others not significant.

Table 4

Papillary thyroid carcinoma properties based on worst preceding FNA diagnosis.

	Malignant	Suspicious for malignancy	Follicular Neoplasm	AUS
Gender *				
Male: Female	41:147	32:150	9:43	13:39
Age (years) *				
≤45	85 (45.2)	72 (39.6)	18 (34.6)	16 (30.8)
>45	103 (54.8)	110 (60.4)	34 (65.4)	36 (69.2)
Mean Tumor Size (cm ±SD) ¶	1.9±1.1	2.0±1.3	2.5±1.6	2.1±1.3
Tumor Stage ^				
T1	83 (44.1)	106 (58.2)	23 (44.2)	35 (67.3)
T1a	25 (30.1)	39 (36.8)	5 (21.7)	11 (31.4)
T1b	58 (69.9)	67 (63.2)	18 (78.3)	24 (68.6)
T2	39 (20.7)	54 (29.7)	23 (44.2)	12 (23.1)
T3	62 (33.0)	19 (10.4)	6 (11.5)	5 (9.6)
T4	4 (2.1)	3 (1.6)	0 (0.0)	0 (0.0)
Lymph Node Metastasis #				
N1	64 (34.0)	9 (4.9)	1 (1.9)	1 (1.9)
N0	78 (41.5)	96 (52.7)	21 (40.4)	26 (50.0)
NX	46 (24.5)	77 (42.3)	30 (57.7)	25 (48.1)
Distant Metastasis (time of surgery) *				
M1	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
MX	186 (98.9)	182 (100)	52 (100)	52 (100)
Lymphovascular Invasion #				
Present	93 (49.5)	26 (14.3)	8 (15.4)	1 (1.9)
Absent	95 (50.5)	156 (85.7)	44 (84.6)	51 (98.1)
Extrathyroidal Extension #				
Present	63 (33.5)	10 (5.5)	0 (0.0)	1 (1.9)
Absent	125 (66.5)	172 (94.5)	52 (100)	51 (98.1)
Multifocal Disease *				
Present	119 (63.3)	96 (52.7)	25 (48.1)	29 (55.8)
Absent	69 (36.7)	86 (47.3)	27 (51.9)	23 (44.2)
Local Recurrence or Late Metastasis §				
Yes	16 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)
No	172 (91.5)	182 (100)	52 (100)	52 (100)
Totals	**188 (100)**	**182 (100)**	**52 (100)**	**52 (100)**

Abbreviations: SD – Standard deviation

Values expressed as number with percent of total following in parentheses.

* Not significant.

¶ P<0.04.

Post hoc pairwise comparison: FOL v M: P<0.02; all others NS.

^P<0.001.
Post hoc pairwise comparison: AUS v M: P=0.001, SUS v M: P<0.001; all others NS.

#P<0.001.
Post hoc pairwise comparison: AUS v M: P<0.001, FOL v M: P<0.001, SUS v M: P<0.001; all others NS.

§P<0.001.
Post hoc pairwise comparison: AUS v M: P<0.02, FOL v M: P<0.02, SUS v M: P<0.001; all others NS.

Table 5

Pathologic Features Stratified by Cytologic Diagnosis and Papillary Carcinoma Subtype

			Cytologic Diagnosis				
Papillary Subtype			**Malignant**	**Suspicious for malignancy**	**Follicular Neoplasm**	**AUS**	**Total**
FV	T Stage	T1	26	80	16	28	150
		T2	14	44	18	11	87
		T3	6	11	4	5	26
		T4	0	1	0	0	1
	Total		46	136	38	44	264
CV	T Stage	T1	42	16	7	7	72
		T2	19	9	4	1	33
		T3	19	3	1	0	23
		T4	1	0	0	0	1
	Total		81	28	12	8	129
High-risk	T Stage	T1	15	10	0	0	25
		T2	6	1	1	0	8
		T3	37	5	1	0	43
		T4	3	2	0	0	5
	Total		61	18	2	0	81
FV	N Stage	N0	24	67	14	23	128
		N1	4	4	1	0	9
	Total		28	71	15	23	137
CV*	N Stage	N0	31	20	6	3	60
		N1	31	1	0	1	33
	Total		62	21	6	4	93
High-risk	N Stage	N0	23	9	1	0	33
		N1	29	4	0	0	33
	Total		52	13	1	0	66
FV*	LVI	Absent	37	122	34	43	236

Papillary Subtype			Cytologic Diagnosis				
			Malignant	Suspicious for malignancy	Follicular Neoplasm	AUS	Total
		Present	9	14	4	1	28
	Total		46	136	38	44	264
CV*	LVI	Absent	46	24	8	8	86
		Present	35	4	4	0	43
	Total		81	28	12	8	129
High-risk *	LVI	Absent	12	10	2	0	24
		Present	49	8	0	0	57
	Total		61	18	2	0	81
FV	ETE	Absent	42	132	38	43	255
		Present	4	4	0	1	9
	Total		46	136	38	44	264
CV*	ETE	Absent	62	26	12	8	108
		Present	19	2	0	0	21
	Total		81	28	12	8	129
High-risk *	ETE	Absent	21	14	2	0	37
		Present	40	4	0	0	44
	Total		61	18	2	0	81
FV	Recur/Met?	No	45	136	38	44	263
		Yes	1	0	0	0	1
	Total		46	136	38	44	264
CV	Recur/Met?	No	74	28	12	8	122
		Yes	7	0	0	0	7
	Total		81	28	12	8	129
High-risk	Recur/Met?	No	53	18	2	0	73
		Yes	8	0	0	0	8
	Total		61	18	2	0	81

Abbreviations: FV – follicular variant; CV – conventional variant; LVI – lymphovascular invasion; ETE – extrathyroidal extension; Recur/Met? – local recurrence and/or metastasis; NS – not significant

*Asterisk denotes statistical significance

T stage: FV (P=0.58, NS), CV (P=0.37, NS), High-risk (P=0.08, NS)
N stage: FV (P=0.15, NS), CV (P<0.001), High-risk (P=0.13, NS)
LVI: FV (P=0.05), CV (P=0.002), High-risk (P=0.001)
ETE: FV (P=0.13, NS), CV (P=.008), High-risk (P=0.001)
Recur/Met?: FV (P=0.32, NS), CV (P=0.08, NS), High-risk (P=0.09, NS)