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Predictive Value of Cytologic Atypia in Indeterminate Thyroid Fine-Needle Aspirate Biopsies

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Abstract

Background—Fine-needle aspiration (FNA) biopsies are the most accurate method for diagnosis of thyroid nodules. Unfortunately, biopsies are indeterminate 15–30% of the time and surgery is thus required for a definitive diagnosis. We aimed to determine whether specific descriptors of cytologic atypia mentioned in indeterminate FNA reports were associated with malignancy on final histopathology.

Methods—Retrospective review of 1000 surgery patients identified 466 indeterminate FNA lesions that underwent either a hemi- or total thyroidectomy between 1998 and 2009. We screened FNA reports for specific descriptors of nuclear atypia. Univariate and multivariate analyses were performed to evaluate the independent effect of cytologic atypia descriptors on the risk of malignancy.

Results—Nuclear atypia on FNA conferred a risk of malignancy of 42% ($P < 0.0001$). Risk of malignancy increased from 17% for zero descriptors to 81.2% when four or more descriptors of atypia were described. Nuclear grooves and inclusions together conferred a risk of malignancy, specificity, and false positive rate of 79.3%, 98.2% and 1.8% respectively.

Conclusions—The presence of four or more descriptors of cytologic atypia or the presence of both nuclear inclusions and grooves together confers a high risk of malignancy on final histopathology and a low false positive rate. These findings should be taken into consideration when interpreting FNA reports and total thyroidectomy should be considered for those patients at higher risk.

Thyroid nodules are common and are being detected more frequently as a result of noninvasive radiographic imaging studies. Though most thyroid nodules are benign, the overall risk of malignancy is approximately 6.2%, and thus detection of a thyroid nodule warrants a diagnostic evaluation. Typically, patients with thyroid nodules proceed to a fine-needle aspiration biopsy (FNA) for diagnosis and determination of treatment. Cytologic evaluation of FNAs can usually render a diagnosis, but 15 to 30% of FNAs are indeterminate.^{1–3} These patients require surgery for a definitive diagnosis. Many groups are

trying to improve the diagnostic capabilities of FNAs; molecular markers such as galectin-3, HBME-1, as well as microRNA and gene expression profiles have all shown promise but are not yet accurate enough to be used clinically.⁴⁻⁶ Thus, there is a need to maximize the prognostic information available from current cytology reports.

Recently, the National Cancer Institute (NCI) issued guidelines to help stratify risk among FNA diagnoses.^{7,8} These guidelines divide FNAs into five possible diagnostic categories with attendant risk for malignancy. Category one is for benign lesions and category five is for indisputably malignant ones. Categories two through four encompass the indeterminate lesions. Biopsies in these categories have some concerning features, but fail to reach the diagnostic standard for malignancy. Group two lesions are called, “Follicular Lesions of Indeterminate Significance/Atypia of Indeterminate Significance” and carry a risk of malignancy of 5–10%. Group three lesions are called, “Follicular Neoplasm/Suspicious for Follicular Neoplasm” and apply to nonpapillary follicular patterns and Hürthle cell lesion and carry a risk of malignancy of 20–30%. Group four lesions are, “Suspicious for Malignancy” and carry a risk of malignancy up to 75%. Of note, the guidelines mention that cytologic atypia is a feature found in both benign and malignant lesions and do not incorporate the presence or absence of atypia into the prognostic framework.

Cytologic atypia is frequently described in FNA reports. It is a feature that raises concern, but the exact risk of specific atypical findings is unknown. Several groups have looked at cytologic atypia in thyroid FNAs. These studies have suggested that the risk of malignancy of cytologic atypia in indeterminate lesions is up to 40%.⁹⁻¹² Currently, most clinicians advocate a hemithyroidectomy in this group of patients to render a definitive diagnosis. If malignancy is identified on the final histopathology report, a completion thyroidectomy is usually warranted, with all the incumbent risks of reoperative surgery. Better prognostic information from FNA cytology, including an interpretation of cytologic atypia, might obviate the need for a second operation in these patients. The significance of atypical findings on FNA cytology, however, has not been fully elucidated.

We hypothesized that individual descriptors of atypia could further differentiate malignant tumors from benign lesions. We therefore compared the risk of malignancy in FNA reports describing atypia to FNAs with no atypia. We aimed to refine the tools available to clinicians in interpreting abnormal FNA reports thereby enabling them to risk-stratify patients more effectively before surgical intervention.

METHODS

This study had the approval of the Institutional Review Board of New York Presbyterian–Weill Cornell Medical Center (NYP-WC). The medical records of surgery patients from the division of Endocrine Surgery at NYP-WC from October 1998 through March 2009 were reviewed. Patients were included in the study if they had an indeterminate FNA biopsy defined by groups two, three and four of the NCI guidelines.⁸ All patients in this study underwent either a hemi- or total thyroidectomy at NYP-WC for both FNA biopsy or symptomatic reasons. Patients were excluded from the study if they had a FNA biopsy that did not require further surgery.

Charts were reviewed by at least two researchers. Patient data including sex, age, details of FNA cytology, cytopathologist, final histopathological diagnosis and tumor size were documented and entered into a computer database. If the patient had more than one FNA biopsy, the most recent results were tabulated. All FNA biopsies were reviewed by a cytopathologist. If the patient had cytology slides from a referring medical center read at NYP-WC, the read from NYP-WC was tabulated.

Cytology was deemed atypical if any of the following descriptors were used in the FNA report: psammomatous calcifications or psammoma bodies; powdery, open, fine, pale or clear chromatin, nuclear clearing, “Orphan Annie Eyed” clear nuclei; nuclear membrane irregularities, irregular nuclear contours, nuclear creases, nuclear folds, nuclear grooves; intranuclear cytoplasmic invaginations, pseudoinclusions, intranuclear inclusions; enlarged nuclei, nuclear enlargement; small, pinpoint or micro nucleoli; peripheral nucleoli; pleomorphism, pleomorphic nuclei; atypia, atypical.

Each qualifying nodule was treated separately in the database. Great care was taken to ensure that sampled nodules and nodules on surgical pathology were appropriately matched by location and size. For instance, if a nodule was found to be a follicular adenoma, but there was an incidental micro papillary thyroid carcinoma (PTC) found elsewhere in the gland, the nodule was classified as benign. However, if a micro-PTC was found within a larger nodule, it was considered malignant.

Each nodule was classified by FNA diagnosis and then by surgical pathology. FNA atypical descriptors were then tabulated for each group. The univariate relationship between the presence of each atypical descriptor and malignancy was assessed by the chi-square test or Fisher’s exact test, as appropriate. The univariate relationship between continuous variables (i.e., age, nodule size, and number of descriptors) and malignancy was assessed by the t-test or Wilcoxon rank-sum test, as appropriate. Multivariate logistic regression was performed to examine the independent effect of age, sex, nodule size, and cytologic atypia on the risk of nodule malignancy (as determined by surgical pathology; malignant vs. benign). All *P* values were two-sided with statistical significance evaluated at the 0.05 alpha levels, and 95% confidence intervals (CI; for adjusted odds ratios, ORs) were calculated to assess the precision of the obtained estimates. All analyses were performed by SPSS, version 15.0 (SPSS, Chicago, IL).

FNA biopsy results were considered true positive or false positive when the presence of atypical descriptors correlated with malignancy or benign tumors on final pathology, respectively. Similarly, the FNA reports were considered true negative or false negative when the absence of cytologic descriptors excluded thyroid cancer or were correlated with malignancy on final histopathology, respectively.

RESULTS

One thousand patients that underwent surgical treatment were found to have 1005 nodules (Fig. 1). Of these nodules, 266 (26%) had benign cytology and 216 (22%) had malignant cytology. Fifty-seven patients (6%) fell into an “other” category. Of these patients, 46 (4.6%) had no FNA and were taken to surgery for Graves disease, nodular Hashimoto disease, or symptomatic goiter. Five patients’ FNAs were nondiagnostic (<1%). For six patients (<1%), we were unable to correlate the sampled nodule with a histological diagnosis. These patients had both benign and malignant disease processes that were not assigned to specific nodules within the thyroid. The remaining 461 patients had 466 nodules that were indeterminate and were defined as the study group.

Eighty-one percent of patients were female and 19% were male. The mean age of the study population was 48.8 years. Upon univariate analysis, there were no differences between benign and malignant groups when looking at sex or average tumor size. However, patients under 30 or older than 69 years of age had a significantly higher risk of malignancy in the study group ($P<0.001$) (Table 1). Final histopathology was benign in 327 nodules (70%) and malignant in 139 (30%) (Table 2).

More than half (56%) of the biopsies were read at NYP-WC and the remainder (44%) were read at referring institutions. A total of 50 medical centers, including both academic and community practices, were represented with 113 individual cytopathologists contributing reports. There were no significant differences in the rate of cytologic atypia or malignancy between academic and community centers. Furthermore, atypical lesions were no more likely to be malignant from academic centers than from their community counterparts ($P=0.68$).

In our study group, 238 nodules (51%) of the 466 indeterminate lesions had nuclear atypia on FNA. Lesions with cytologic atypia were more likely to be malignant compared to lesions without (42% vs. 18%, respectively, $P=0.0001$). The sensitivity and specificity of atypia on FNA were 71% and 57%, respectively. Nuclear clearing ($P=0.0002$), nuclear grooves ($P=0.0001$), intranuclear inclusions ($P=0.0001$), oval nuclei ($P=0.0014$), pinpoint nucleoli ($P=0.025$), or pleomorphism ($P=0.0489$) were all more likely to be malignant compared to benign lesions on univariate analysis (Table 3).

A subset multivariate analysis of descriptors among the 238 nodules with atypia was performed to assess the independent risk of each descriptor on malignant diagnosis. The presence of nuclear grooves (OR = 2.03, 95% CI = 1.121–3.683; $P=0.019$) and nuclear inclusions (OR = 2.61, 95% CI = 1.28–5.32; $P=0.008$) were shown to be significantly related to malignancy. Oval nuclei (OR = 2.9, 95% CI = 0.714–11.887; $P=0.136$) and pleomorphism (OR = 2.183, 95% CI = 0.64–7.44; $P=0.212$) demonstrated nonsignificant trends toward greater malignancy risk (Table 3).

The risk of malignancy for the independent variables in atypical lesions, nuclear grooves and nuclear inclusions was 55% and 65%, respectively. When they were combined in a single nodule the risk of malignancy was 79.3%. Although, the presence of nuclear grooves and inclusions had a low sensitivity, their presence showed a high specificity, 98.2%, and a very low false positive rate, 1.8% (Table 4).

The more atypical descriptors there were in a report, the more likely a nodule was malignant. The risk of malignancy was 17% for zero descriptors, 41.8% for one or more, 50% for two or more, 53.7% for three or more, and 81.2% for four or more descriptors. The OR for malignancy in the presence of two or more descriptors when compared to one or fewer was 3.14 (95% CI = 1.99–4.95; $P<0.0001$).

In patients with one or more descriptors of atypia, 99 of the 139 (71.2%) malignant tumors were true positives; however, under the same conditions, 138 of the 327 (42.3%) benign lesions were false positives on FNA. In the same way, patients who had two or more descriptors of atypia, 51 of the 139 (36.7%) malignant tumors were true positive, but 51 of the 327 (15.6%) benign lesions were incorrectly identified as malignant on FNA. When three or more descriptors were present, 22 of the 139 (15.8%) tumors were correctly identified. Additionally, only 19 out of 326 (5.8%) benign lesions were false positives on FNA. On the other hand, when four or more descriptors were present 13 of the 139 (9.4%) malignant tumors were correctly identified, but only 3 of the 327 (0.9%) benign lesions were misdiagnosed as malignant. Therefore, an increasing number of descriptors characterized lesions that were more likely to be malignant on final histopathology. Although an increase in specificity was found as more descriptors of atypia were described on FNA, the sensitivity decreased as a result of an increase in false-negatives rates (Table 5).

In the study population, 185 of 466 (40%) nodules carried the microfollicle descriptor. Of these, 145 (78%) were benign and 40 (22%) were malignant. Two-hundred eighty one (60%) of the lesions did not have microfollicles; of these 182 (65%) were benign and 99 (35%) were malignant. This difference was significant ($P=0.0019$) suggesting that the

presence of microfollicles does not confer a higher likelihood of malignancy in thyroid lesions. Thirty-seven of 466 nodules were described as hypercellular (8%). No significant differences were seen for hypercellular lesions.

DISCUSSION

Thyroid nodules are a common problem for which the standard investigative tool—FNA—is an imperfect test. There are a substantial number of nodules that cannot be adequately classified as benign or malignant on the basis of the FNA result. Atypia is frequently described in thyroid cytology reports, but the implications of an atypical reading are poorly quantified. Here we have attempted to refine the ability to predict malignancy on the basis of the inclusion of atypia in the cytology report from thyroid fine needle aspiration.

Consistent with prior studies, our data showed that age was greatly correlated with higher risk of malignancy in indeterminate lesions. The risk of malignancy jumped to 50% for patients younger than 30 and 42% for patients older than 69 compared to all other age groups with a malignancy rate of approximately 25%. However, contrary to previous reports, sex did not correlate with malignancy.¹³ Of note, 47% of our study population was found to have indeterminate lesions, which is higher than our quoted 15 to 30% for all thyroid FNAs. This is because all of our patients went to surgery and does not include non-surgical patients with benign lesions.

Our findings indicated that cytologic atypia on FNAs of thyroid nodules increased the risk of malignancy from 18% to 42%. This result is consistent with data published by Goldstein et al., who found a 44% risk of malignancy in FNAs of thyroid nodules with cytologic atypia.⁹ In general, the malignancy rate of cytologic atypia on FNA biopsies varies among different studies. Kelman et al., and Miller et al. showed a very high malignancy rate associated with atypia, 60% and 71% respectively, whereas McHenry et al. reported a malignancy rate of 28% on FNAs with cytologic atypia.^{10,11,14} However, most of these studies are small series, from seven to 52 atypical nodules, and none looked at the risk of individual descriptors.

The designation of indeterminate lesions on thyroid FNA reports remains a challenge given the varying incidence of malignancy and elusive guidelines for management. As mentioned earlier, the guidelines do not correlate atypia as a prognostic factor. Therefore, most of the patients with an indeterminate lesion require a hemithyroidectomy to render a definitive diagnosis. As such, patients who undergo a diagnostic hemithyroidectomy are commonly subjected to a second surgical procedure (completion thyroidectomy) if the final histopathology reveals malignancy. This two-stage approach adds increased morbidity to the patient, heightens patient anxiety, and increases the economic burden on the health care system. Thus, a more accurate initial assessment of the risk of malignancy is highly desirable.

Our study suggested that the presence of four or more descriptors in the cytology report, or the presence of nuclear inclusions and grooves together increased the risk of malignancy to 80%. These findings may differ from Lubitz et al. and Maruta et al. who recently looked at cytological features of follicular neoplasms.^{15,16} They both reported a correlation between nuclear grooves and inclusions with malignancy but did not identify them as independent predictors factors. Of note, their studies focused on the differentiation of follicular carcinoma from follicular adenoma on cytology and this is the study population for which they selected. In our study, 43% of indeterminate lesions were classic papillary thyroid cancer and 32% follicular variant of papillary thyroid cancer on final pathology. Only 13% were follicular carcinomas. In our data, follicular lesions were more likely to be a variant of

papillary thyroid cancer on final pathology than follicular carcinoma. Therefore, nuclear grooves and inclusions played a more important role in this analysis.

Recent advances in molecular genetics of thyroid cancer could be applied to permit a better prediction of malignancy in the nodules with indeterminate cytology. Recently, Nikiforov et al, showed that the presence of mutations in the BRAF, RET/PTC, and RAS families were a strong indicator of cancer because 97% of mutation-positive nodules had a malignant diagnosis on final histopathology.¹⁷ Our group had previously differentiated benign and malignant thyroid nodules at the molecular level by microarray profile.^{6,18} These data indicate that molecular testing of thyroid indeterminate lesions for a panel of mutations could be performed in a clinical setting. However, these techniques require further validation.

Our study had four main limitations. First, intraobserver variability is a known phenomenon when interpreting thyroid FNA biopsies and had the potential to skew our results.^{19,20} By including the work of more than 100 cytopathologists, we hoped to minimize the vagaries of individual pathologists, but some risk remains. Second, there was a very low incidence of nondiagnostic lesions in this study (<1%) because most FNA biopsies were performed outside the institution. Therefore, our group typically evaluated only indeterminate diagnostic biopsies. Most prior studies report a nondiagnostic specimen rate of 5–15%.²¹ Though this does create a sampling bias, it did not affect the results of this study as our focus was on evaluation of indeterminate lesions. Thirdly, there was a wide range of FNA diagnoses under the umbrella of “indeterminate lesions,” including Hürthle cell lesions, follicular lesions and lesions suspicious for PTC. Despite including 466 nodules, the study was underpowered to assess the risk of individual atypical descriptors within these subcategories. None showed statistical significance in our analyses. Finally, this was a retrospective study at a single institution. Larger prospective studies are warranted to further validate the risk of atypia in FNA indeterminate lesions.

In summary, cytologic atypia in thyroid nodule FNAs is associated with an increased risk of malignancy. More descriptors conferred a greater risk of malignancy. The risk is particularly high for patients having both nuclear grooves and inclusions. Given this, clinicians and patients could consider a total thyroidectomy rather than a hemithyroidectomy when the cytologic report indicates the presence of these groups. This analysis provides clinicians with a more sophisticated set of tools to help guide decisions when interpreting FNA reports and ultimately may facilitate a more accurate assessment and treatment of patients with thyroid nodules.

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FIG. 1.
Breakdown of study population

TABLE 1

Clinical breakdown of study population

Characteristic	Benign	Malignant	<i>P</i> value
Sex			
Male	63 (70.0%)	27 (30.0%)	0.995
Female	264 (70.3%)	112 (29.7%)	
Age (y) *			
19–29	16 (50.0%)	16 (50.0%)	<0.001
30–39	72 (66.7%)	36 (33.3%)	0.065
40–49	82 (75.3%)	27 (24.7%)	0.945
50–59	79 (74.5%)	27 (25.5%)	0.908
60–69	57 (76.0%)	18 (24.0%)	0.817
70–89	21 (58.3%)	15 (41.7%)	<0.001
Mean tumor size (cm)	2.50 (0.3–7.4)	2.55 (0.2–11.0)	0.91

*
P value based on a relative risk of malignancy of 25% in FNA results

TABLE 2

Surgical pathology for 466 nodules in the study group

Benign (<i>n</i> = 326) (70%)	
Nodular hyperplasia	157 (48%)
Follicular adenoma	119 (36%)
Hürthle cell adenoma	30 (9%)
Thyroiditis/Hashimoto disease	17 (5%)
Graves disease	2 (<1%)
Benign thyroid cyst	1 (<1%)
Oncocytic parathyroid nodule	1 (<1%)
Malignant (<i>n</i> = 139) (30%)	
PTC	60 (43%)
FVPTC	45 (32%)
FTC	18 (13%)
Hürthle cell carcinoma	7 (5%)
Mixed PTC/FVPTC	6 (4%)
Anaplastic carcinoma	1 (<1%)
Medullary carcinoma	1 (<1%)
Poorly differentiated carcinoma	1 (<1%)

PTC papillary thyroid cancer, *FVPTC* follicular variant of papillary thyroid carcinoma, *FTC* follicular carcinoma

TABLE 3Breakdown of atypical descriptors for total study population ($n = 237$)^a

Descriptor	Benign ($n = 137$)	Malignant ($n = 100$)	<i>P</i> value
Psammoma bodies	2 (<1%)	2 (1%)	NS
Nuclear clearing	27 (8%)	30 (22%)	0.0002
Nuclear grooves (OR = 2.03, 95% CI = 1.121–3.683; $P = 0.019$)	41 (13%)	50 (36%)	0.0001
Nuclear inclusions (OR = 2.61, 95% CI = 1.28–5.32; $P = 0.008$)	16 (5%)	30 (22%)	0.0001
Enlarged nuclei	52 (16%)	25 (18%)	NS
Oval nuclei	3 (1%)	9 (6%)	0.0014
Pinpoint nuclei	1 (<%)	15 (11%)	0.025
Peripheral nuclei	1 (<%)	1 (<1%)	NS
Pleomorphism	5 (1.5%)	7 (5%)	0.049
Atypia not otherwise specified	47 (14%)	25 (18%)	NS

^aIf the descriptor is also shown to bear significant risk on multivariate analysis, ORs, 95% CIs, and *P* values are also presented

NS non-significant

TABLE 4

Sensitivity, specificity, risk of malignancy, and false-positive rate for number of cytologic atypia descriptors in all sampled nodules ($n = 466$)

	One or more (%)	Two or more (%)	Three or more (%)	Four or more (%)
Sensitivity	71.2	36.7	15.8	9.3
Specificity	57.6	84.3	94.2	99.1
Risk of malignancy	41.7	50	53.4	81.2
False-positive rate	42.3	15.64	5.8	0.92

TABLE 5

Sensitivity, specificity, risk of malignancy and false-positive rate for nuclear grooves and nuclear inclusions, and four or more descriptors ($n = 466$)

Characteristic (%)	Nuclear grooves (%)	Nuclear inclusions (%)	Both (%)
Sensitivity	50	30	16.55
Specificity	70	88	98.2
Risk of malignancy	55	65	79.3
False-positive rate	30	12	1.8