The new National Cancer Institute classification system for fine-needle aspiration cytology is an excellent standard for reporting cytology results

SUMMARY

BACKGROUND

On October 22 and 23, 2007, the National Cancer Institute (NCI) hosted the "NCI Thyroid Fine Needle Aspiration State of the Science Conference" which brought together a group of national experts in the field who reviewed the literature and attended the meeting. Among the many important features of the meeting was the general acceptance of a classification scheme for FNA cytology. The aim of the study by Theoharis and associates was to report their experience with this new NCI six-tier cytology classification and to analyze the distribution of diagnostic categories in their patients and to evaluate the diagnostic accuracy of the NCI conference recommendations for the classification for FNA cytology.

METHODS AND PATIENTS

In January 2008, the authors' institution adopted the NCI classification for reporting thyroid FNA cytology results as suggested at the NCI conference. This prospective study extended over a 12-month period, during which the incidence and histologic outcomes of each diagnostic category was examined. The study comprised 3207 consecutive FNA thyroid cytology specimens evaluated at the Yale-New Haven Hospital from January 1st, 2008 through December 31, 2008, some of which were submitted by outside laboratories for a second opinion. The majority of the FNAs were performed under ultrasound guidance.

The surgical histology report was the standard for confirming the accuracy of the diagnostic FNA cytology classification. The specificity of the FNA cytology was estimated using two approaches. One was to consider the FNA as a diagnostic test if the FNA specimens were interpreted as suspicious of malignancy or positive for malignancy, and the remaining categories were classified as negative. The other approach was to consider the FNA as a screening test if the FNA cytology specimens were diagnosed as benign or negative, and the remaining FNA cytology categories were classified as positive. Cases classified as unsatisfactory or indeterminate were excluded from calculations for both approaches because they indicate the absence of diagnostic material and the need for additional sampling rather than the presence of malignancy or benign cytology. Also excluded from calculations in the first approach—FNA as a diagnostic test—were follicular or Hürthle cell adenomas because cytology does not distinguish this group from their malignant counterparts.

RESULTS

A total of 3207 thyroid FNAs obtained from 2468 patients were evaluated at the authors' institution during the 12-month study, and FNA specimens from 271 patients (11%) were submitted by outside laboratories for a second opinion. Of the 3207 thyroid
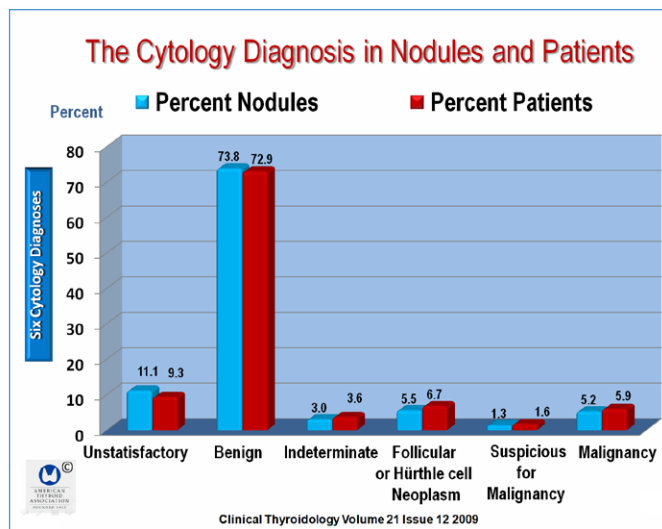

Figure 1. This figure shows the correlation of six cytology diagnoses with the histology diagnosis. The six diagnostic cytology categories are (1)Unsatisfactory/ (2) Benign/negative, (3) Indeterminate/cells of undetermined significance, (4) follicular neoplasms/Hürthle cell neoplasms or (5) suspicious for malignancy and (6) malignant. The benign histologic categories are (1) multinodular goiter, Hashimoto's thyroiditis, follicular and Hürthle cell adenoma. The malignant categories are papillary thyroid carcinoma, follicular thyroid carcinoma, medullary carcinoma and squamous cell carcinoma of the head and neck. The number of patients shown in this figure represents a consolidation of the malignant and benign histology groups. The data for this figure is derived from Table 2 of Theoharis et al.
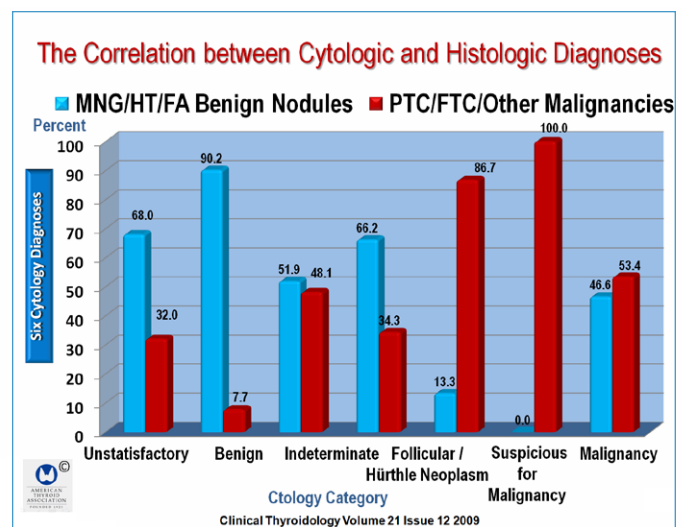

Figure 2. This figure shows the correlation between the cytology and histologic diagnoses. MNG = multinodular goiter; HT = Hashimoto's thyroiditis; FA = follicular adenoma; PTC = papillary thyroid carcinoma, FTC = follicular thyroid carcinoma; Other = other thyroid cancers.

nodules, 2386 (74%) were negative for malignancy. Of the 2468 patients, 378 (15%) had a thyroidectomy. Of this group of 2468 patients, 82 had thyroidectomy (3%) because of other clinical considerations such as the size of the nodules, a family history of thyroid cancer or a history of neck irradiation, and the majority (75%) had nodular goiters, followed by lymphocytic thyroiditis and colloid nodules (74%), and 13 (16%) had follicular adenoma and 8 had papillary thyroid carcinoma (10%). All of the papillary thyroid carcinomas that were discovered in a histologic specimen in patients with benign cytologic diagnosis had tumors ≤10 cm, 6 of which were 0.5 cm or less. Among the patients who had FNA, 89 had indeterminate FNA cytology, 58 of which (65%) were further subclassified as low cellularity with microfollicular architecture and absence of colloid and, and 31 (35%) had nuclear features not characteristic of benign cytology. Seventeen of the 89 (19%) patients had a repeat FNA, which was unsatisfactory in 3, negative for malignancy in 11, indeterminate in 1, follicular neoplasm in 1, negative for malignant in 11, indeterminate in 1 and positive for papillary thyroid carcinoma in 1.

Of the 230 patients with an unsatisfactory diagnosis, repeat FNA was performed in 34 (15%) patients. Repeat FNA diagnoses were unsatisfactory in 14 patients, negative for malignancy in 19, and positive for papillary thyroid carcinoma in 1 patient. Of the 230 patients, 25 (11%) with an unsatisfactory FNA had a surgical resection, which revealed a benign goiter in 9 patients, follicular adenoma in 8, and papillary thyroid carcinoma in 7 patients.

The distribution of six-tier FNA cytology diagnoses in nodules (Figure1)

This figure shows the cytology diagnosis in terms of nodules and patients. The six cytology diagnoses were: (1) unsatisfactory in 357 of 3207 nodules, (11.%), (2) benign or negative in

2368 (74%), (3) indeterminate or cells of undetermined significance (3%), (4) follicular or Hürthle cell neoplasms (6%), (5) suspicious for malignancy (1%), and malignant (5%). (Percentages are rounded to an integer in the text but shown in full in the figures). Of the 3720 thyroid nodules in the study, the cytology interpretation was negative for malignancy in 357 (11%), benign or negative in 2368 (74%), indeterminate or cells of undetermined significance in 95 (3%), follicular nodules or Hürthle cell neoplasm in 176 (6%), or suspicious for malignancy in 43 (1%), and malignant in 168 (5%). (Figure 1)

The correlation between FNA cytology and histology diagnoses (Figure2)

The study found excellent correlations between the FNA diagnostic categories and the histologic outcomes in predicting nonneoplastic versus neoplastic thyroid nodules and benign vs. malignant thyroid nodules.
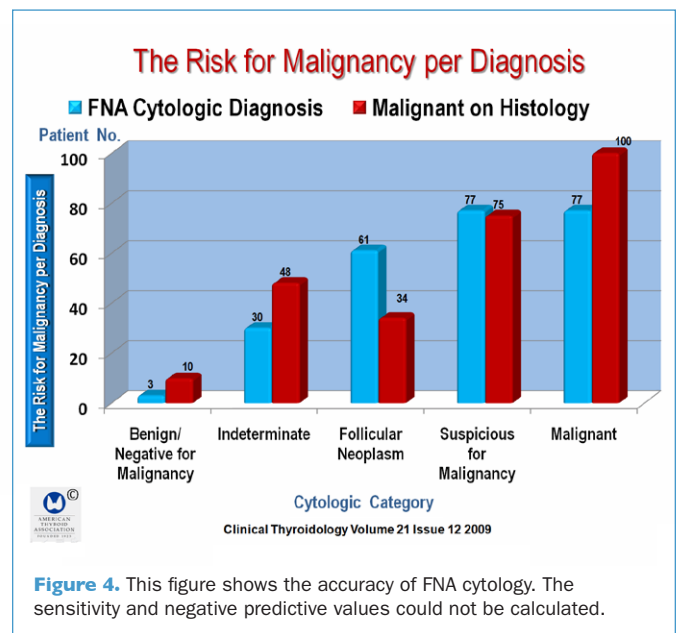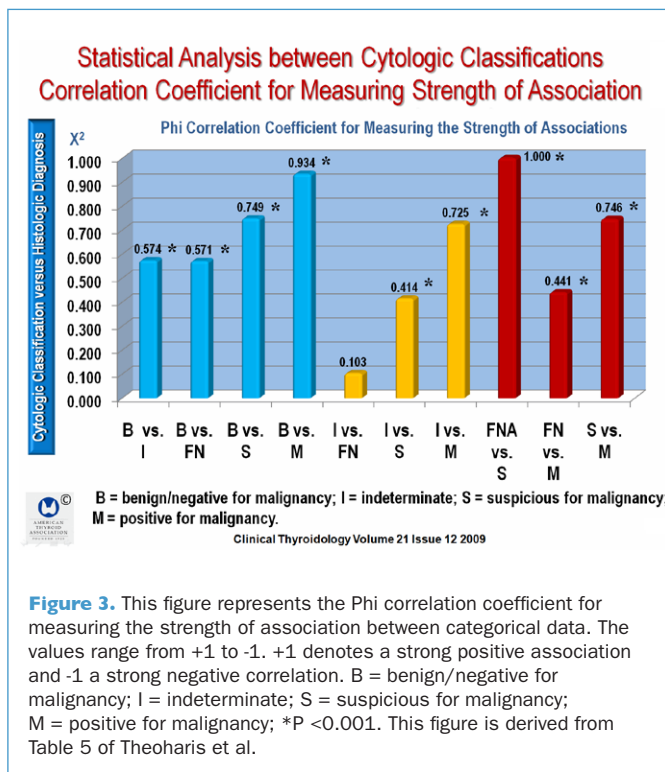
Statistical analysis of the cytologic classification system (Figure3)
Overall, 378 (15%) of the patients

Comparing each individual cytologic diagnostic category against the other four categories included in the analysis (without follicular or Hürthle cell adenomas) found statistically significant differences between benign and indeterminate, benign and follicular neoplasms, benign and suspicious, indeterminate and malignant, follicular neoplasms and malignant as well as suspicious and malignant. On the other hand, there was no statistically significant difference between indeterminant and follicular neoplasms.

The risk of malignancy per diagnosis (Figure 4)

There was an excellent association between the FNA categories and in predicting benign versus malignant thyroid nodules (p<0.0001). The cytology diagnosis in five of the thyroid FNA categories was compared with the histology findings in 82 patients who had surgery. Among the benign/negative for malignancy cytology group that comprised 82 of the 2468 patients (3%), 8 of the 82 had malignant tumors (9.8%) on histology; of the Indeterminate/cells of undetermined

Figure 3. This figure represents the Phi correlation coefficient for measuring the strength of association between categorical data. The values range from +1 to -1. +1 denotes a strong positive association and -1 a strong negative correlation. B = benign/negative for malignancy; I = indeterminate; S = suspicious for malignancy; M = positive for malignancy; *P <0.001. This figure is derived from Table 5 of Theoharis et al.

Figure 4. This figure shows the accuracy of FNA cytology. The sensitivity and negative predictive values could not be calculated.

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significance cytology group that comprised 27 of 89 patients (30%), 13 of 27 (48%) had malignant tumors; of the follicular

Figure 5. The false-negative rate could not be calculated because of the small number of patients with benign diagnosis who underwent surgery. The false-positive rates were 2.2%, but the FNA cytologies were all categorized as suspicious. Because only 15% of the patients underwent surgery, the sensitivity of thyroid FNA for diagnosing malignant thyroid nodules could not be calculated, nor could the sensitivity of thyroid FNA cytology be accurately assessed as a screening test for all neoplasms.

neoplasm cytology group that comprised 102 of 166 patients (61%), 35 of 102 patients (34%) had malignant histology; of the suspicious for malignancy cytology group, which comprised 30 of 39 patients (77%), 26 of 30 (75%) had malignant histology; and lastly, among the positive for malignancy cytology group, which comprised 112 of 145 patients (77%), 112 of 112 (100%) had malignant histology (Figure 4).
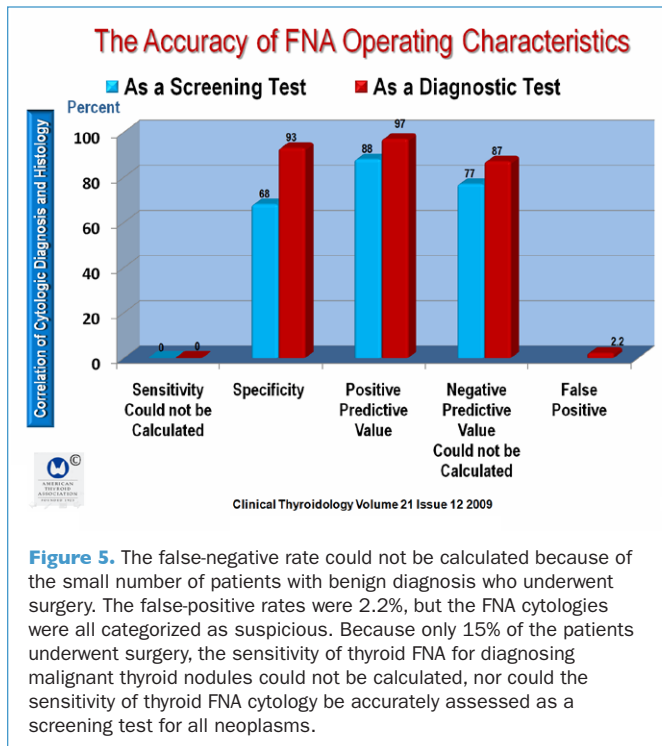
The accuracy of cytology (Figure 5)

Based on the small number of patients with benign diagnoses, the false-negative rate could not be calculated. The false-positive rate was 2.2%, all of which were diagnosed as suspicious cytology. Because only 15% of the patients had surgery, the FNA sensitivity for diagnosing malignant thyroid nodules could not be accurately calculated, nor could the sensitivity of thyroid FNA as a screening test for all neoplasms be accurately estimated. The specificity for a diagnosis of malignant thyroid nodules was 93%, whereas the specificity as a screening test for all neoplasms was 68%. The positive predictive values for a follicular neoplasm, suspicious, and positive cytologic diagnoses were 34%, 87%, and 100%, respectively. (Figure 5)

CONCLUSION

This study demonstrates that the recently proposed NCI classification system for FNA cytology is an excellent standard for reporting thyroid FNA results. Each diagnostic category conveys specific risks of malignancy, which offers guidance for patient management.

COMMENTARY

Several recent clinical guidelines address the evaluation of thyroid nodules, many of which suggest that a tiered system for classifying thyroid FNA cytology provides the most accurate diagnostic approach(1) (2). The NCI conference has proposed diagnostic categories for the classification of (FNA) cytology, comprising the following categories: (1) Nondiagnostic, Benign, (2) Atypia of Undetermined Significance, (3) Follicular Neoplasm or suspicious for a follicular neoplasm, (4) Follicular Neoplasm or Suspicious for a Follicular Neoplasm, (5) Suspicious for Malignancy, and (6) Malignant. The contents of this very important meeting are available on the National Cancer Institute website (http://thyroidfna.cancer.gov/ and has been reviewed by several authors. (1;3;4) Cibus et al. point out that it is critical that the cytopathologist communicate thyroid FNA interpretations to the referring physician in terms that are succinct, unambiguous, and clinically helpful. This is especially important considering that the terminology for thyroid FNA has varied significantly in recent years from one laboratory to another, creating confusion in some instances and hindering the sharing of clinically meaningful data among multiple institutions.

The study by Theoharis CG, and associates is one of the early studies of the accuracy of the National Cancer Institute Thyroid Fine-Needle Aspiration State-of-the-Science Conference that opens new avenues of information for the biopsy and interpretation of FNA cytology.

Theoharis and associates found an excellent association between the FNA categories and the predictions of benign versus malignant thyroid nodules (p<0.0001). However, the false-negative rate could not be calculated because of the small number of patients with benign diagnosis who underwent surgery. The false-positive rates were 2.2%, but the FNA cytologies were all categorized as suspicious. Because only 15% of the patients underwent surgery, the sensitivity of thyroid FNA for diagnosing malignant thyroid nodules could not be calculated, nor could the sensitivity of thyroid FNA cytology be accurately assessed as a screening test for all neoplasms. However, of considerable importance, the specificity for diagnosing malignant thyroid nodules was 93%, whereas the specificity as a screening test for all neoplasms was 68%. The positive predictive values for a follicular neoplasm, suspicious, and positive cytologic diagnosis were 34%, 87%, and 100%, respectively. The authors' conclusion that their data demonstrate the recently proposed NCI classification system is excellent for reporting thyroid FNAs is well supported by this study.

Yang et al(5) reported their experience with a similar FNA cytology classification from 2 institutions in which cytology diagnoses were classified as unsatisfactory, benign, atypical cellular lesion (ACL), follicular neoplasm (FN), suspicious for malignancy, and positive for malignancy. Of 4703 FNA samples, 10.4% were classified as unsatisfactory, 64.6% were classified as benign, 3.2% were classified as ACL, 11.6% were classified as FN, 2.6% were classified as suspicious, and 7.6% were classified as

malignant. At least 1 repeat FNA was necessary in 512 patients, mainly for results in the unsatisfactory and ACL categories. Of this group, 1252 patients had surgical follow-up, including 14.9% with unsatisfactory FNA results, 9.8% with benign results, 40.6% of with ACL results, and 63.1% with FNA results, 86.1% with suspicious results, and 79.3% with malignancy results. Sources of errors were diagnoses on inadequate specimens, sampling errors, and overlapping cytologic features between hyperplastic nodules and follicular adenoma. The sensitivity and specificity of thyroid FNA for the diagnosis of malignancy were 94% and 98.5%, respectively. The authors concluded that FNA provides an accurate diagnosis of thyroid malignancy, and that 6 diagnostic categories were beneficial for triaging patients for either clinical follow-up or surgical management

This relatively new evidence supports the NCI recommendations for the interpretation of FNA cytology.

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