

The Indeterminate Thyroid Fine-Needle Aspiration

Experience From an Academic Center Using Terminology Similar to That Proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference

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BACKGROUND: To date, thyroid fine-needle aspiration (FNA) has been used by clinicians as the screening test of choice to determine whether surgery is required and this is what the pathology report should communicate. Standard terminology for reporting thyroid FNA has not been implemented yet, and pathologists have used various reporting systems to communicate results. A significant source of confusion among both pathologists and clinicians has been the use of the indeterminate category. On the basis of an analysis of 1150 thyroid FNAs in 2000, this institution modified the reporting of thyroid biopsy results into 6 categories, including unsatisfactory. The indeterminate category was separated into 3 subgroups: 1) indeterminate for neoplasia (IND), 2) follicular neoplasm (FN), and 3) suspicious for malignancy (SUSP). Repeat FNA in 6 months to 12 months was recommended for IND and surgery for FN and SUSP categories. **METHODS:** To determine the validity of this approach, the outcomes of this reporting system from July of 2000 to December of 2006 were analyzed. The IND category was used for 2 subsets of cases: (a) those that morphologically fall into the gray zone between adenomatoid nodule (AN) and FN, for Hurthle cell nodule (hyperplasia vs neoplasm), and chronic lymphocytic thyroiditis with concern for neoplasia; and (b) for suboptimal specimens due to low epithelial cellularity or collection artifacts. **RESULTS:** Among 5194 thyroid nodules, the IND category comprised 18%. FNA follow-up was done in 21% of IND cases: 58% were benign/negative and did not require surgery based on cytology alone. Surgical follow-up in 46% of IND showed 52% were benign/negative, and 42% were follicular/Hurthle cell adenomas. The surgical yield of malignancy in IND was low (6%) when compared with the FN category, which was 14% (more than 2× that of the IND category), and the SUSP category, which was 53% (almost 9× that of the IND category). **CONCLUSIONS:** A 6-tier reporting system for thyroid FNA was effective for determining which patients needed surgery versus follow-up FNA and also guided the clinician on the extent of surgery. *Cancer (Cancer Cytopathol)* 2009;117:195-202. © 2009 American Cancer Society.

KEY WORDS: thyroid cancer, reporting system, management guidelines, fine-needle aspiration, biopsy.

The American Thyroid Association (ATA)¹ and The American Association of Clinical Endocrinologists (AACE)² management guidelines from 2006 lump follicular lesions, follicular neoplasm (FN), and

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suspicious for malignancy (SUSP) diagnostic categories under the indeterminate for malignancy category and suggest surgery for all these patients, quoting a malignancy rate of approximately 20% for an indeterminate FNA. In an attempt to standardize the reporting system for thyroid FNA, the National Cancer Institute (NCI) hosted a multidisciplinary Thyroid State of the Science Conference in Bethesda, Maryland, in October 2007.³ The consensus from this conference has suggested a 6-tier reporting system, with the use of 3 categories Atypia of undetermined significance (AUS), suspicious for follicular neoplasm/suspicious for Hurthle cell neoplasm, and suspicious for malignancy—to report thyroid aspirates that fall between the negative/benign and positive/malignant diagnostic categories.

We have been using a 6-tier reporting system, including 3 categories—IND (equivalent to AUS), FN (equivalent to suspicious for FN), and SUSP—between benign and malignant since the year 2001 after having reanalyzed our thyroid biopsy data and outcomes from January 1997 through June 2000.^{4,5} We subsequently validated the value of repeat FNA in the follow-up of the IND category versus surgery in the FN and SUSP categories based on malignancy outcomes in these 3 indeterminate areas of thyroid cytology over an additional 3.5-year period.⁶ In this communication, we present the details of our reporting terminology and outcome-based follow-up over a 6.5-year period, with an emphasis on the indeterminate categories. Our approach is similar to that being proposed by the 2007 NCI conference in an attempt to standardize thyroid cytology reporting and correlate it with management guidelines.^{3,7}

MATERIALS AND METHODS

Thyroid biopsies are performed in interventional radiology (approximately 63%) with on-site evaluation by cytopathology and the majority of the remainder by 3 endocrine and ear-nose-throat surgeons. We use smears, both air-dried Diff Quik and alcohol-fixed Papanicolaou stained preparations, for all FNAs. Thyroid biopsies performed in interventional radiology may have accompanying core biopsies (CB) if deemed necessary for adequacy. Our experience with the combined FNA/CB crush preparation approach is detailed in a separate publication.⁸

We retrieved all thyroid biopsy reports from our computerized files for the period between July 2000 and December 2006. During this time, all the cytopathologists were using similar reporting terminology for thyroid FNA. The 6 cytologic diagnostic categories used by us are unsatisfactory, negative for malignancy, indeterminate for neoplasm, neoplasm, suspicious for malignancy, and malignancy. Before October 2002, in our previous laboratory information system, a diagnostic category was not mandatory; thus, these were assigned by us based on the descriptive report for the period July 2000 to September 2002. Several adequacy criteria for thyroid FNA have been proposed in the literature.^{3,9-13} We use the Papanicolaou Society of Cytopathology Task Force criteria,¹³ which are similar to those proposed recently at NCI.³ If many follicular cells are present in single cell pattern or there are less than 6 cell clusters in the presence of abundant colloid, the FNA is still considered to be adequate. Thyroiditis does not require a minimum number of follicular cells.

The category of negative for malignancy shows abundant colloid, mixed follicular, and Hurthle cells mainly in a macrofollicular pattern or as flat sheets, without crowding or nuclear atypia. Involutional changes such as histiocytes, hemorrhage, calcification, mesenchymal repair, and fibrosis may be present. Thyroiditis is classified as negative if there is no associated concern for neoplasia.

The indeterminate for neoplasm (IND) category is used for cases with adequate epithelial cellularity that show scant to moderate colloid, predominantly a single cell type/monotonous population (follicular cells or Hurthle cells) admixed with a small percentage of the other epithelial cell type, showing a macro- and microfollicular pattern, and possibly some nuclear chromatin clearing, crowding, and/or nuclear overlapping. The differential diagnosis in these cases includes hyperplasia, follicular neoplasm, less often follicular variant of papillary carcinoma, and rarely chronic lymphocytic thyroiditis (CLT) with concern for concurrent neoplasia. Predominantly cystic or colloid-rich lesions with rare/absent follicular cells, cases with excess blood and low cellularity with a predominant microfollicular pattern, cases with extensive clotting or other artifacts are detailed as such in the IND category and follow-up FNA is requested in 6 months to 12 months.

Table 1. Distribution of 5194 Thyroid Biopsies by Categories From July 2000 Through December 2006

Cytology Diagnosis	Total Number of Cases	Number of Resected Cases	Surgical Follow-up		
			Negative for Malignancy	Neoplasm	Positive for Malignancy
Unsatisfactory	274 (5%)	70	54 (77%)	10 (14%)	6 (9%)
Negative for malignancy	3337 (64%)	357	294 (82%)	57 (16%)	6 (2%)
Indeterminate for neoplasm	924 (18%)	430	224 (52%)	181 (42%)	25 (6%)
“Morphologic”	767	383	196	169	18
“Adequacy related”	157	47	28	12	7
Neoplasm	307 (6%)	248	61 (25%)	151 (61%)	36 (14%)
Suspicious for malignancy	97 (2%)	83	19* (23%)	20 (24%)	44 (53%)
Positive for malignancy	255 (5%)	225	5 (2%)	3 (1%)	217 (97%)

* Of these cases, 32% had chronic lymphocytic thyroiditis.

The neoplasm category includes follicular/Hurthle neoplasms and typically shows scant colloid, a monotonous population of either follicular or Hurthle cells in a predominantly (>80%) microfollicular pattern, and cells with nuclear crowding and overlap.

The suspicious for malignancy category demonstrates 1 or more, but not all, of the following: non-Hurthle cells with grooves and/or intranuclear cytoplasmic inclusions, nuclear elongation, and chromatin clearing. These changes are worrisome but not diagnostic of papillary carcinoma.

Malignant cytology is defined as diagnostic of papillary carcinoma, medullary carcinoma, anaplastic carcinoma, lymphoma, or metastatic malignancy.

RESULTS

We have an annual laboratory volume of approximately 52,000 specimens, with 4800 FNAs, 9000 nongynecologic, and 38,000 gynecologic specimens. During the 6.5-year period July of 2000 to December of 2006, 5780 biopsy specimens from 5194 thyroid nodules were interpreted by our department. The average breakup by diagnostic categories for 5194 nodules based on the worst FNA interpretation for each nodule was unsatisfactory 5%, negative 64%, indeterminate for neoplasia 18%, follicular neoplasm 6%, suspicious for malignancy 2%, and malignant 5% (Table 1). A total of 1583 of 5194 (30%) of thyroid nodules had at least 1 abnormal FNA result, of which 986 (62%) had surgical resection. Follow-up histology showed that 676 (69%) nodules were neoplastic, of which 52% were follicular/Hurthle cell adenomas and

48% were malignant. Our overall surgical yield of malignancy by patient (not nodules) was 28%, and the false negative rate was 0.16%.

For analysis of the IND category, 924 of 5194 (18%) cases, we separated the most common morphologic IND cases (83% of all our IND)—follicular hyperplasia versus neoplasia, Hurthle cell nodule—hyperplastic versus neoplastic and CLT with concern for concurrent neoplasia (767 cases) from the adequacy-related IND cases (157 cases, 17% of all IND) that included clotted specimens with entrapped follicular cells, few or no follicular cells, cyst contents, colloid-rich lesions, and bloody specimens with scant cellularity and a microfollicular pattern (Fig. 1).

Among 767 of 5194 nodules that were classified as morphologic IND, FNA follow-up was done in 144 of the nodules diagnosed on initial FNA as morphologic IND and a definitive diagnosis was obtained in 62%. Seventy-seven of 144 (54%) of the follow-up FNAs were benign, and these patients did not require surgery based on cytology alone (Table 2). On repeat FNA, 45 (31%) remained IND, of which 26 had surgery and 12% were malignant. Surgical follow-up was available in 383 of 767 (50%) of this IND subgroup; 51% were negative (AN/CLT), and 44% were follicular/Hurthle cell adenomas (Table 3). The surgical yield of malignancy was 5%, approximately 2.5× our negative FNA category (Table 1). For comparison, in the FN diagnostic category, consisting of 248 of 307 (81%) cases with surgical follow-up, the surgical yield of malignancy was 14%, 25% were negative (AN/CLT), and 61% were adenomas. In the SUSP category, consisting of 83 of 97 (86%) cases with surgical

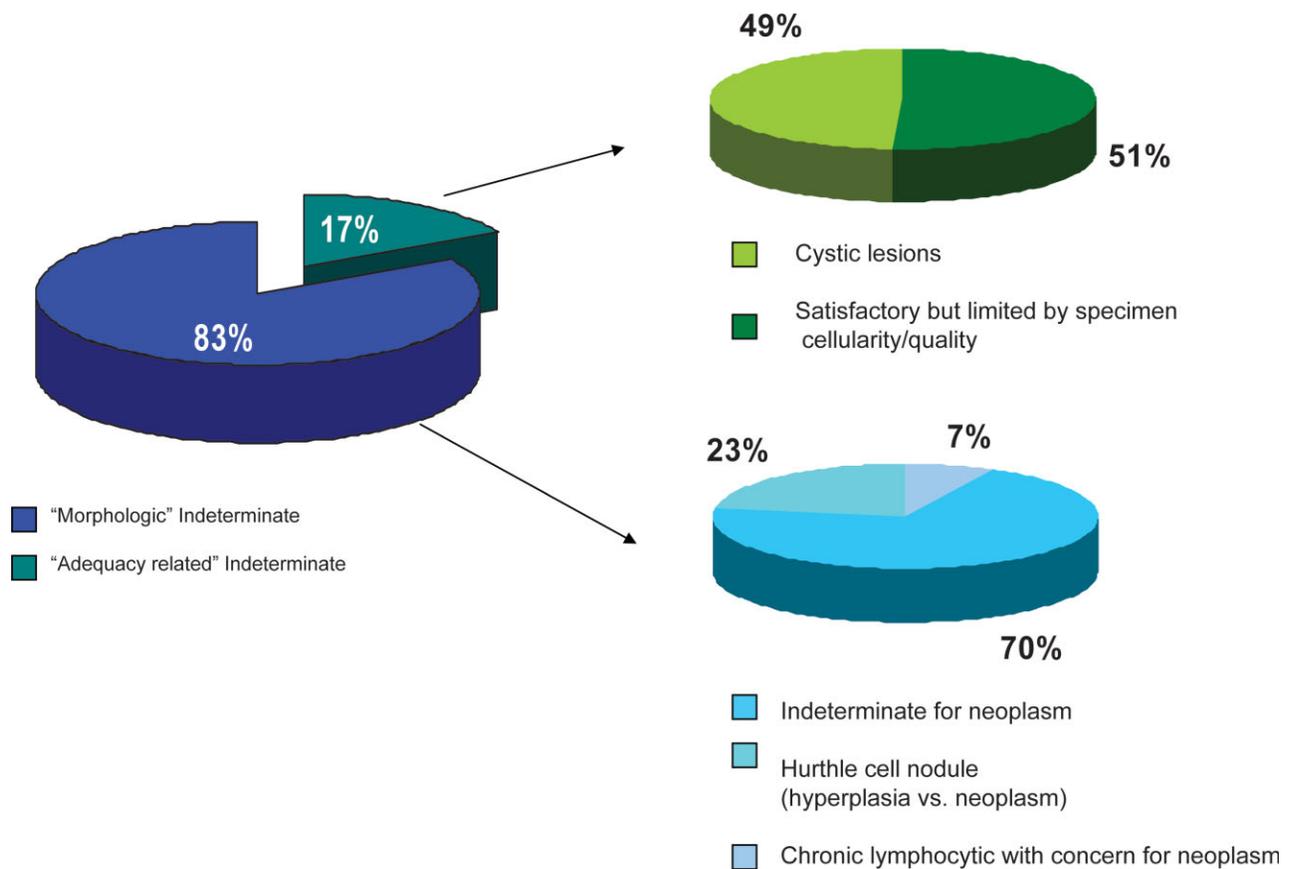


FIGURE 1. Indeterminate subcategories for 924 cases from July 2000 through December 2006.

Table 2. FNA Follow-up of 144 Cases Diagnosed by First FNA as Morphologic Indeterminate Cases From July 2000 Through December 2006

Repeat FNA for Indeterminate for Neoplasm	1/2 2000-2006	Surgical Outcome			
		Surgical f/u	Negative	Neoplasm	Positive
Total Cases 144	144				
Unsatisfactory (%)	10 (7%)	4	3	1	0
Negative for malignancy (%)	77 (54%)	14	9	4	1
Indeterminate for neoplasm (%)	45 (31%)	26	10	13	3
Neoplasm (%)	9 (6%)	7	2	4	1
Suspicious for malignancy (%)	1 (<1%)	1	1*	0	0
Positive for malignancy (%)	2 (1%)	2	0	1†	1

FNA indicates fine-needle aspiration.
 * Parathyroid gland.
 † Follicular adenoma with atypia.

follow-up, the surgical yield of malignancy was 53%, approximately 9× that of the IND category (40 [91%] papillary thyroid carcinoma, 1 minimally invasive Hurthle cell carcinoma, 1 Hurthle cell neoplasm of low malignant potential, and 2 medullary carcinomas), 23%

were negative (32% with CLT), and 24% were adenomas (Table 1).

Among the remaining 157 of 5192 adequacy-related IND cases, follow-up FNA was performed in 49 (31%) nodules; a definitive diagnosis was obtained in 82%: 14%

remained IND and 4% were unsatisfactory. Histologic follow-up was available in 30%. Among 18 cases of cyst contents, there was 1 malignancy; however, among the suboptimal specimens (entrapment of follicular cells in fibrin clot or air-drying artifacts), 6 of 29 cases had malignant histology: papillary carcinoma (1 case),² and follicular carcinoma (5 cases, including 3 minimally invasive and 1 low malignant potential; Table 4).

Table 3. Histology Follow-up of Morphologic Indeterminate for Neoplasm Cases From July 2000 Through December 2006

Surgical follow-up for indeterminate for neoplasm	1/2 2000-2006
Total cases 383 of 767	
Negative for malignancy (%)	196 (51%)
Neoplasm (%)	169* (44%)
Follicular adenoma	146
Hurthle cell adenoma	24*
Positive for malignancy (%)	18 (5%)
Papillary carcinoma	12
Follicular carcinoma	6†

*Includes cases signed by surgical pathologists as Hurthle cell nodule.
 †Includes 5 follicular carcinomas with minimal invasion and 1 Hurthle cell carcinoma with minimal invasion.

Comparison of our 3 indeterminate diagnostic categories (IND, FN, and SUSP) in Table 5, shows a marked difference in the subsequent incidence of malignancy.

DISCUSSION

Pathologists have varied widely in how they report thyroid FNA. In 2006, Wang performed an excellent, comprehensive review of the published literature on thyroid reporting, including the simplistic 2 category classification of benign/malignant and those with 6 or more categories containing 1 or more layers of uncertainty between benign and malignant.¹⁴ Needless to say, this lack of consistency in reporting thyroid FNA has led to wide variances in sensitivity and specificity calculations depending on what one considers to be true and false positives/negatives and resulted in confusion among clinicians on how to manage patients who do not have a clear-cut negative or positive thyroid FNA result. For the clinician and patient, 2 questions need to be answered by the thyroid biopsy report: 1) Does the patient need surgery? 2) If yes, what should be the extent of surgery? More recently, follow-up FNA in indeterminate lesions has been increasingly used. Thus, it becomes important that the pathologist's communication is clear and that clinicians are aware of the

Table 4. Follow-up of Adequacy-related Indeterminate for Neoplasm Cases From July 2000 Through December 2006

Follow-up FNA/Outcome	Satisfactory for Evaluation but Limited by Scant Cellularity/Poor Cell Preservation	Cystic Lesions
49 cases	27 cases	22 cases
Unsatisfactory (%)	0 (0%)	2 (9%)
Negative for malignancy (%)	19 (70%)	16 (73%)
Indeterminate for neoplasm (%)	3 (11%)	4 (18%)
Neoplasm (%)	5 (19%)	0 (0%)
Suspicious for malignancy (%)	0 (0%)	0 (0%)
Positive for malignancy (%)	0 (0%)	0 (0%)
Histology Follow-up/Outcome		
47 of 157 cases	29 cases	18 cases
Negative for malignancy (%)	16 (55%)	12 (67%)
Neoplasm (%)	7* (24%)	5 (28%)
Follicular adenoma	7*	5
Hurthle cell adenoma	0	0
Positive for malignancy	6† (21%)	1 (5%)
Papillary carcinoma	2	1
Follicular carcinoma	5†	0

* Includes 1 trabecular adenoma.
 † There were 3 FCA with minimal invasion and 1 follicular tumor of low malignant potential.

Table 5. Follow-up for the Gray Zone From July 2000 Through December 2006

Cytology	Indeterminate for Neoplasm	Neoplasm	Suspicious for Malignancy
Surgical follow-up			
Number of cases:	430	248	83
Non-neoplastic	224 (52%)	61 (25%)	19 (23%)
Neoplasm			
Benign	181 (42%)	151* (61%)	20* (24%)
Malignant	25 (6%)	36 (14%)	44† (53%)

* Included 1 Hurthle cell nodule (surgical).

† Included 1 follicular neoplasm of low malignant potential.

significance of the terminology and the outcomes of the diagnostic categories used by the pathologists reporting thyroid FNA at their institution.

Follicular lesions are the most problematic as far as precise cytologic, or for that matter histologic, classification is concerned. Although the inability to distinguish follicular adenoma from follicular carcinoma is an inherent limitation of cytologic evaluation, it is possible to separate follicular/Hurthle cell lesions with a single cell population, often in a predominant microfollicular pattern, as a neoplasm. The NCI terminology recommends the term suspicious for follicular neoplasm for this category. In most institutions, such cases will have a lobectomy if the nodule is solitary.⁷ In our experience, the surgical yield of the neoplasm category is 75% neoplastic and 14% of these neoplasms are malignant (Tables 1 and 5). The incidence of follicular carcinoma is currently estimated to be much lower than previously described,¹⁵ and a high percentage of malignancies in the neoplasm category are found to be follicular variants of papillary carcinoma. If the FNA shows focal features of papillary carcinoma or there is a predominant insular pattern, pathologists may place such FN cases into the suspicious for malignancy category or retain them in the neoplasm category, depending on the level/degree of suspicion.¹⁶ Either way, the patient will have surgery but may need a completion thyroidectomy if a lobectomy is done initially. We include Hurthle cell neoplasm in the neoplasm category, specifying the cell type, and have not found any significant difference in malignancy yield in Hurthle cell neoplasm versus follicular neoplasm categories.

The other well known gray zones in follicular lesions are the distinction between follicular hyperplasia (AN)

and follicular patterned neoplasms and the Hurthle cell nodule for which the differential is hyperplasia in the setting of an adenomatous or thyroiditis gland versus a Hurthle cell neoplasm. These cases comprise the majority of our IND cases. A smaller number of cases include biopsies with CLT for which the cytologic changes/morphology is worrisome but not sufficient to warrant a FN or SUSP categorization (Fig. 1). We have shown that follow-up FNA is negative in 54% of these type of IND cases, avoiding the need for surgery (Table 2). Even in patients that went to surgery, 51% of IND nodules were benign/negative (AN/CLT). Our clinicians are increasingly taking note of our recommendation to follow-up patients in the IND category by repeat FNA (Table 2), based on seeing our consistent outcomes over the past many years.⁴⁻⁶ Among our patients who remained IND on repeat FNA (31%), 58% had follow-up surgery. The rate of neoplasia was 50%, and the rate of malignancy was 12%, similar to the outcome of our neoplasm cases, supporting that surgery is justified in this subgroup.

Thyroid FNA is a sensitive and highly specific test for the diagnosis of papillary carcinoma. Pathologist's experience and comfort level is paramount in first recognizing which cases are concerning for papillary carcinoma, and then placing them appropriately, based on level of suspicion of malignancy, into either the AUS neoplasm, or suspicious for malignancy categories. In our experience, the majority of cases that fall short of a definitive diagnosis of papillary carcinoma due to quantitative and/or qualitative reasons are classified as SUSP and less often as FN. We rarely classify these cases as IND. Our outcomes reflect this—the rate of malignancy by cytologic category is 97% for malignant, 53% for SUSP (of which 91% are

papillary carcinomas), 14% for FN (of which 58% are papillary carcinomas), and 6% for the IND category (of which 58% are papillary carcinomas) (Table 1).

The majority of pathology laboratories use air-dried or alcohol-fixed smears to assess thyroid FNA. Pathologists may receive specimens that are suboptimal either due to the nature of the lesion (vascular, predominantly cystic, fibrotic) or operator inexperience. Where should and where do pathologists currently categorize these specimens? We include predominantly cystic lesions aspirated under ultrasound with almost total collapse of lesion, colloid-rich lesions with rare to no follicular cells, and bloody cases with few microfollicles in the IND category; however, the uncertainty in these cases is related to adequacy and not morphology. In our reporting system, we have a statement of adequacy and a diagnostic category that precedes the descriptive diagnosis; suboptimal specimens are detailed as satisfactory but limited by . . . (reason), under the adequacy statement so that the clinician is aware of why the patient needs follow-up. These adequacy-related IND cases comprised 17% of our IND category (Fig. 1). We have recommended repeat FNA of unsatisfactory lesions in 2 to 3 months and of adequacy-related IND lesions in 6 to 12 months, and subsequently obtained a more definitive diagnosis in the majority of these cases. The rate of malignancy in our adequacy-related IND cases was higher than the morphologic IND cases, emphasizing the need for this categorization and subsequent follow-up of suboptimal cases due to artifacts (Table 4). By adequacy number criteria, such specimens are not unsatisfactory, and classifying them as negative is not appropriate because they need follow-up irrespective of clinical indications. Raab et al have emphasized that suboptimal specimens can be a significant source of false negatives in thyroid cytology.¹⁷

Yassa et al¹⁸ have published their experience with a long-term multidisciplinary approach to thyroid nodule evaluation. They use a 6-tier reporting terminology similar to ours, and in a review of 2587 subsequent patients, AUS composed 6%, FN 8%, and SUSP 8% of all initial cytodiagnostic categories. Based on final FNA, the surgical yield of malignancy was 24% for AUS, 28% for FN, 60% for SUSP, and their overall surgical yield of malignancy in patients going to surgery was 53%. There are some differences between the analysis and data from Yassa et al and our study. Yassa et al only included thyroid nod-

ules ≥ 1 cm in size, the cytologic preparation used was exclusively ThinPrep, and the entities included in their AUS category and the surgical yield of neoplasia were not described in detail. In a study by Yang et al¹⁹ involving a review of 4703 thyroid FNAs from 2 institutions also using a 6-tier reporting terminology, AUS composed 3.2% of interpretations, FN 11.6%, and SUSP 2.6%; the yield of malignancy was 13.5%, 32.2%, and 64.7%, respectively. Neither of these studies describes how suboptimal FNA specimens were interpreted. However, because the rate of FN and unsatisfactory aspirates is higher in these studies, it is likely that we are placing more cases into the IND/AUS categories, explaining our higher AUS rate (18%). Our approach has been to maximize sensitivity of thyroid FNA, and we have an overall 69% rate of neoplasia and 28% rate of malignancy in patients going to surgery; our false negative rate is 0.16%. If we remove the adequacy-related IND, which are likely classified as unsatisfactory or benign in other institutions, our IND composes 14% of thyroid FNA. With an increasing number of incidental follicular/Hurthle cell neoplasms being biopsied, we have seen an expected increase in the IND/FN categories over the past few years.

The NCI conference guidelines suggest AUS for the category we have described as IND. AUS is defined as a heterogeneous category that may be appropriate to use for architectural or cytologic atypia or a compromised specimen. It includes the gray zone follicular/Hurthle cell lesions as well as offers the option of placing suboptimal specimens (air-drying, clotting, low epithelial cellularity), atypical cyst lining/mesenchymal cells (repair), therapy changes, and other nonspecific cytologic changes that cause concern into this category.³ The recommendation is that this category be followed by correlation with clinical/radiologic findings and repeat FNA at an appropriate interval.⁷ As for any atypical diagnosis in pathology, AUS should be used judiciously in thyroid FNA. However, use of standardized criteria and terminology as well as follow-up and outcome-based data are required over a considerable period of time and in varied practice settings to suggest a realistic estimate of the percentage of thyroid biopsies that are expected to fall into the AUS, FN, and SUSP categories. The upcoming 2009 publication of the NCI terminology by means of an atlas and Web site, in a format similar to that used for the Bethesda system for

reporting cervical cytology,^{20,21} represents an major step forward to standardization of thyroid FNA reporting.

At the NCI thyroid conference, providing data on the risk of malignancy in thyroid diagnostic categories within the cytology report was discussed but was left as optional in the final summation.⁷ It is important that larger volume centers determine their own malignancy rates as relates to thyroid reporting categories so that they may share them with their clinicians. We have done this systematically over the past 8 years in a multidisciplinary setting and shown that repeat FNA is a safe follow-up protocol for AUS/IND thyroid biopsies and prevents unnecessary surgery in at least half of these cases. In conclusion, a 6-tier reporting system, when used in a well defined and consistent manner, especially in gray zone areas of thyroid cytopathology, allows appropriate triage to FNA versus surgery based on the significant difference in the risk of subsequent malignancy in the 3 indeterminate categories.

Conflict of Interest Disclosures

The authors made no disclosures.

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