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Fine Needle Aspiration of the Thyroid: A Cytohistologic Correlation and Study of Discrepant Cases

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Objective: Fine needle aspiration (FNA) is a reliable method in the initial assessment of thyroid nodules. The purpose of this study was to evaluate the causes for discordance between the interpretation on FNA and the pathologic findings in the resected thyroid. *Methods:* A computer search of all thyroidectomy specimens with previous FNA from January 1998 to December 2001 was obtained from the files of the Lauren V. Ackerman laboratory of surgical pathology, Barnes-Jewish Hospital. Excluded from the study were those FNAs performed for suspected and confirmed metastatic disease to the thyroid as well as those cases unavailable for review. A total of 45 FNA cases were identified with cytologic and histologic discrepancies. *Results:* Of the 1253 individual thyroid FNA performed during the study period, 255 patients (20%) subsequently had an open surgical procedure on the thyroid. Of those who underwent surgery, 196 cases (77%) were concordant, whereas 45 patients (18%) were discordant, and 14 cases were excluded due to unavailability of slides for review (for example, returned consult slides). The causes of the 45 discordant cases were: 20 cases (44%) were unsatisfactory for diagnosis, 14 cases (31%) were due to interpretation error (false positive), and 11 cases (24%) were due to sampling error (false negative). *Conclusions:* The most common causes of our discrepant cases are those whose FNA diagnosis was interpreted as "unsatisfactory for diagnosis," in 20 (7.8%) of 255 surgical cases. The false negative rate due to sampling error in 11 (4%) of 255 cases was mainly due to the presence of microscopic papillary thyroid carcinoma (PTC); the false positive rate was due to interpretation error in 14 (6%) of 255 cases, and those were explained by the occurrence of overlapping cytologic features among adenomatous nodules, follicular neoplasms, the follicular variant of PTC, and Hashimoto's thyroiditis.

Introduction

FINE NEEDLE ASPIRATION (FNA) of the thyroid has become the most noninvasive, cost-effective, and efficient method of differentiating benign and malignant thyroid nodules (1). It has a high degree of proven sensitivity and specificity but with a false negative interpretation that averages from 1 to 6% (2,3). According to the Papanicolaou Society of Cytopathology Task Force on Standards of Practice, a false negative (FN) rate not to exceed 2% and a false positive (FP) rate of no more than 3% are regarded as benchmarks that should be achieved on FNA cytology of the thyroid (4). This study, as several others in the recent past, has not reached the level of sensitivity and specificity proposed by the task force. We tried to identify the causes of our discrepant cytologic/histopathologic cases and to identify our FN and FP rates in a patient population where 20% of all patients with prior thyroid FNA underwent a total or subtotal resection of the thyroid gland.

Materials and Methods

A computer search of all FNA of the thyroid from January 1998 to December 2001 was performed at Barnes-Jewish Hospital, Washington University Medical Center, St. Louis, Missouri. During this four-year period, 1253 FNA of the thyroid were performed. These cases included FNA of the thyroid performed by radiologists (ultrasound guidance), cytopathologists (by palpation), and clinicians (by palpation). Of these, 255 patients (20% of the total series of 1253 cases) went to surgery and provided the opportunity for cytologic-histopathologic correlation. Of those, 196 (77% of 255 cases) had cytologic-histopathologic correlation. There were 45 cases (18% of 255 cases) with cytologic-histopathologic discrepancies and 14 cases were excluded due to unavailability of slides for review (returned slides from consultation cases). A total of 45 cases from 45 patients formed the basis for this study (Figs. 1 and 2).

Each patient underwent three separate FNAs, for which

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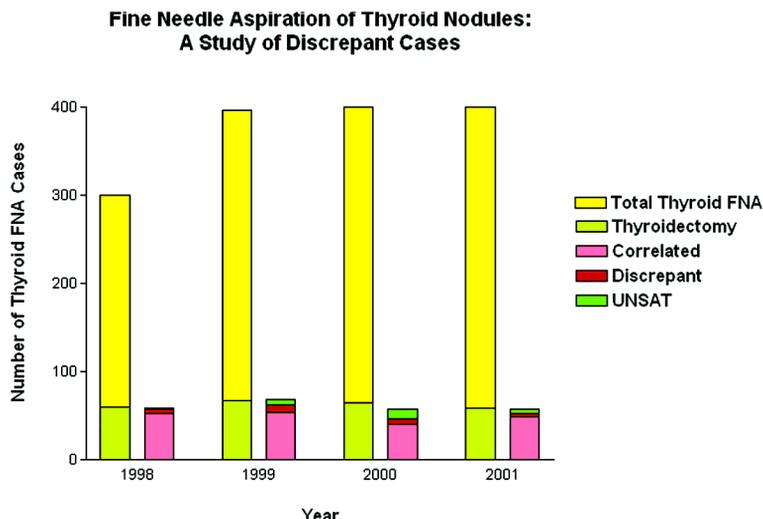


FIG. 1. Of the 1253 cases of thyroid FNA performed at our institution over a period of 4 years, 255 (20%) were taken to surgery. One-hundred-ninety-six (77%) had cytohistologic correlation and 45 (18%) had cytohistologic discrepancies. Fourteen cases were excluded due to unavailability of slides for review. This rate has not significantly changed over the 4 years.

two smears and four slides were prepared from each aspirate. Air dried smears were stained with DiffQuik¹ Dade Behring Newark, DE and alcohol-fixed smears were stained with the Papanicolaou stain. A total of 12 initial slides were made for each patient. When a repeat procedure is necessary for an initial unsatisfactory aspirate, two additional FNAs are done from which two smears and four slides are additionally made. Some clinicians, however, elect not to repeat an "unsatisfactory" aspirate.

The cytologic and histologic sections were reviewed. Causes of our false negative and false positive cases were evaluated and rates were calculated. These rates were determined on the basis of definitions established by the Papanicolaou Society of Cytopathology (4). Accordingly, a false-negative diagnosis was defined as a cytologic interpre-

tation of a non-neoplastic lesion which would otherwise not have had required surgical excision, yet the resection revealed a malignant lesion. A false-positive diagnosis has been defined as a cytologic diagnosis of a neoplasm requiring surgical excision, but revealed to be a non-neoplastic lesion in the surgical resection (4). These rates are then compared to several prior series of thyroid FNA.

Cases with inadequate cytologic samples were not included in the calculation of false-negative cases as these cases were interpreted as "unsatisfactory for diagnosis" and were all reported to the clinicians and radiologists as "preliminary" diagnoses. A repeat FNA is always suggested or offered to the patient for an initial "unsatisfactory for diagnosis." A minimum requirement of 6 to 8 follicular groups with 8-10 follicular cells per group in at least 2 separate aspirates were used

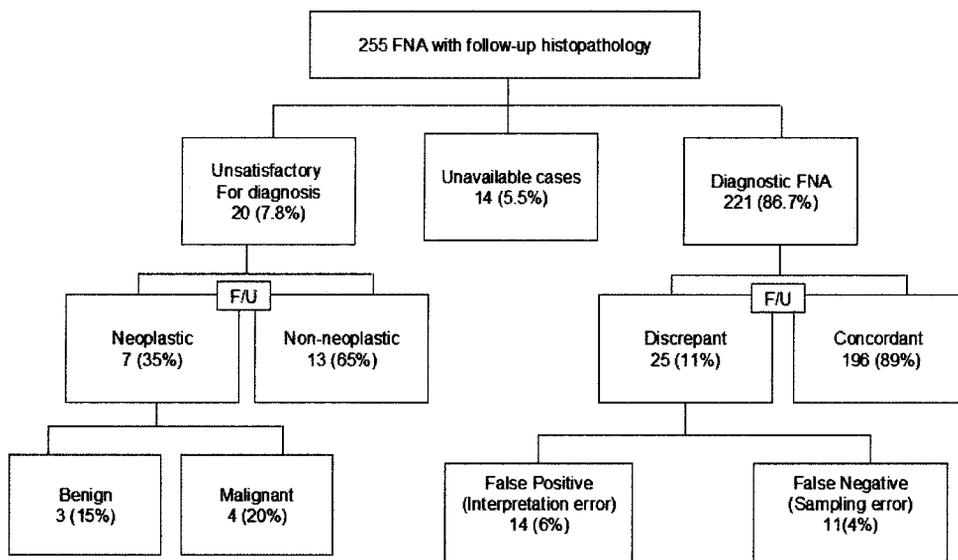


FIG. 2. Flow chart of cases with cytologic-histopathologic correlation.

TABLE 1. HISTOLOGIC DIAGNOSES OF CASES SIGNED-OUT AS "UNSATISFACTORY FOR DIAGNOSIS"

| Number of cases (n = 20) | Percent | Histologic diagnosis |
|-----------------------------|---------|-----------------------------|
| 11 | 55% | Nodular hyperplasia |
| 4 | 20% | Papillary thyroid carcinoma |
| 3 | 15% | Follicular adenoma |
| 1 | 5% | Hashimoto's thyroiditis |
| 1 | 5% | Graves' disease |

for assessment of adequacy in all thyroid FNA samples per site (5). Although an aspirate lacking follicular epithelium can be interpreted as benign colloid nodules in the presence of abundant colloid, aspirates containing only blood in the absence of colloid are considered "unsatisfactory" (6).

The diagnostic categories used at our institution are: "negative for malignancy" for an unequivocal diagnosis of non-neoplastic lesions such as nodular hyperplasia, colloid nodules, and Hashimoto's thyroiditis; "atypical cytology" for follicular lesions with a differential diagnosis of follicular neoplasm or which carry other cytologic features that are indeterminate for neoplasm; "suspicious for malignancy" for cases with rare cells with cytologic features of papillary, medullary or anaplastic thyroid carcinoma; and positive for malignancy- for cases with abundant cells with unequivocal cytologic features of the same malignant neoplasms including other variants of PTC. A comment section is added if a differential diagnosis is provided in any one of these categories. Most surgeons have elected to operate on those cases with a threshold interpretation of "atypical cytology" in our institution.

Results

Of the 45 cases in our final study group, 20 (43%) were "unsatisfactory for diagnosis"; eleven of these 20 (55%) cases were performed by clinicians, seven (35%) were performed by radiologists and two (10%) by cytopathologists. Only two

cases were repeated (still unsatisfactory on the second attempts). All of these patients went to surgery after an "unsatisfactory" interpretation. The ultimate histopathologic diagnosis in these cases included nodular hyperplasia or goitrogenous thyroid (11 cases, 55%), PTC (4 cases, 20%), follicular adenoma (3 cases, 15%), Hashimoto's thyroiditis (1 case, 5%), and Grave's disease (1 case, 5%) (Table 1). The unsatisfactory rate at our institution when a strict criteria of adequacy is applied is 7.8% ($n = 255$).

Eleven discrepant cases were on the basis of sampling error. Most sampling errors were due to the presence of a micropapillary thyroid carcinoma not sampled during the FNA. These cases included: micropapillary carcinoma (PTC < 0.9 cm in diameter) (5 cases), PTC, classic pattern (3 cases), follicular variant of PTC (2 cases), and follicular carcinoma (1 case) (Table 2). Two cases of the follicular variant of PTC only showed rare nuclear grooves on rare cells which was a cause of a FN diagnosis (Fig. 3). There was abundant colloid in the background.

The remaining 14 cases represented interpretation errors: all 14 cases were benign processes whose features mimicked or suggested a neoplasm: Hashimoto's thyroiditis (5 cases), nodular hyperplasia (3 cases), Hurthle cell changes within nodular hyperplasia (3 cases) and follicular adenoma (3 cases) (Table 3).

Four of five cases diagnosed as follicular neoplasms were found to be due to Hashimoto's thyroiditis. The cytologic diagnosis of follicular neoplasm was made on the basis of finding follicles in a background of obscuring blood in four cases and in only one case were there lymphocytes and plasma cells in the aspirates. In cases for which a diagnosis of atypical cytology (3 cases), PTC or suspicious for PTC (3 cases), or Hurthle cell neoplasm (2 cases) was made on the basis of finding nuclear grooves in some of the cells and in some Hurthle cells with a concomitant absence of colloid (Fig. 4). One case diagnosed as a follicular neoplasm which was eventually found to be nodular hyperplasia was based on the presence of numerous follicles and lack of colloid on the aspirate. This was in part due to sampling.

The false positive and false negative rates are calculated at 6% and 4%, respectively, on the basis of these findings.

TABLE 2. CAUSES OF OUR "FALSE NEGATIVE" CASES (SAMPLING ERROR)

| Number of cases (n = 11) | Cytologic diagnosis | Histologic diagnosis |
|-----------------------------|--|--|
| 5 | Nodular hyperplasia Nodular hyperplasia Nodular hyperplasia Follicular lesion Hemorrhagic cyst | Micropapillary TC (1 mm) Micropapillary TC (0.9 and 0.5 cm) Micropapillary TC (1 mm) Micropapillary TC (1 mm) Micropapillary TC (6 mm) |
| 3 | NH with Hurthle cell change Hurthle cell lesion Nodular hyperplasia | PTC PTC arising in a Hashimoto's thyroiditis PTC |
| 2 | Follicular lesion Parathyroid tissue sampled | Follicular variant of PTC Follicular variant of PTC |
| 1 | Nodular hyperplasia | Follicular carcinoma |

PTC, papillary thyroid carcinoma; NH, nodular hyperplasia; TC, thyroid carcinoma.

This calculation is based only on those cases for which there is a confirmatory histopathology.

Discussion

Detection of most PTC, medullary, anaplastic and, in some cases, insular carcinomas of the thyroid on FNA can be done with a degree of sensitivity and specificity (7).² However, a small proportion of cases qualify for the categories of "false positive" and "false negative" due to the nature of the lesion, intrinsic limitations of the procedure, and in most instances, the manner, skill, and experience of the individual operators. Every effort should be made to evaluate the various individual group practices, to determine whether one's results are comparable to national standards and to ascertain whether other methods of practice have affected these reported values.

One national cytopathology society has published guidelines for the standards of practice in FNA cytology of the thyroid (4). These guidelines suggest that a false negative (FN) and false positive (FP) rate of less than 2% and 3%, respectively, should be achieved. These rates were based on several studies published from 1980–1993 (8–15). More recent studies, specifically looking at the individual institution's causes of FN and FP cases, have reported higher and possibly more current realistic rates (9,16–21). This could be a reflection of a higher frequency of surgical excisions of thyroid nodules status-post FNA in recent years as indicated by the fact that approximately 20% of all cases come to resection of a thyroid nodule after an FNA procedure whereas it has only been 10% or so in the past (Table 4).

Individual FP and FN rates have also increased in more recent series (9,16–21). These values have trended upward, especially in the category of FP diagnoses. The causes of this increase in FP diagnoses can be due to the existence of overlapping cytologic features among follicular neoplasms, adenomatous nodules, lymphocytic thyroiditis and some follicular variants of PTC that were less well appreciated in the

past. The presence of nuclear grooves among Hurthle cells in some cases of chronic lymphocytic thyroiditis and nodular hyperplasia is the most frequent cause of FP cases in our series. Overlapping cytologic features can also be seen between nodular hyperplasia and "follicular lesions" for which the differential diagnosis includes a follicular neoplasm, especially if the aspirate does not yield abundant colloid. In five of our cases which showed Hashimoto's thyroiditis on final histopathology, the presence of lymphocytes were only appreciated on FNA in one case which was also bloody and shows absence of colloid. In cases for which an FNA diagnosis of neoplasm such as PTC, follicular neoplasm and Hurthle cell neoplasm, the histopathologic diagnosis was nodular hyperplasia in three cases, Hurthle cell adenoma in three cases and follicular adenoma in three cases. This occurred because of presence of nuclear grooves and concomitant absence of colloid in the aspirates. Therefore, the presence of nuclear grooves with a concomitant absence of colloid are non-specific features which can be seen in cases of Hashimoto's thyroiditis, nodular hyperplasia with oncocytes, follicular adenoma, and Hurthle cell adenoma. These features were also observed by Settakorn, and associates, for which differentiating features between an adenomatous goiter versus follicular neoplasm, adenomatous goiter versus PTC, and thyroiditis versus follicular neoplasm can be demonstratively difficult and confounding (17). These observations and problems are consistent with our own experience. Similar difficulties in the differentiation of adenomatoid nodules, follicular neoplasms and the follicular variant of PTC were also observed by Sidawy et al. (7).

In the FN category, the most common cause in our series is the presence of an unsampled microcarcinoma in the setting of an adenomatous goiter. These PTCs usually measures less than 1 cm in diameter. Four of our cases have been incidental micronodules for which the target lesion is something other than the incidental PTC. One of the cases, however, was an unsampled 0.9 cm nodule in a non-ultrasound guided FNA of an adenomatous goiter. Some pathologists

TABLE 3. CAUSES OF OUR "FALSE POSITIVE CASES" (INTERPRETATION ERRORS)

| <i>Number of cases (n = 14)</i> | <i>Cytologic diagnosis</i> | <i>Histologic diagnosis</i> |
|-------------------------------------|--|---|
| 5 | Follicular neoplasm Follicular neoplasm Follicular neoplasm Follicular neoplasm AC due to NG | Hashimoto's thyroiditis Hashimoto's thyroiditis Hashimoto's thyroiditis Hashimoto's thyroiditis Hashimoto's thyroiditis |
| 3 | PTC Follicular neoplasm AC due to NG | Nodular hyperplasia Nodular hyperplasia Nodular hyperplasia |
| 3 | AC, Hashimoto's thyroiditis Follicular neoplasm, HC type Hurthle cell neoplasm | Hurthle cell adenoma Hurthle cell metaplasia in NH Hurthle cell metaplasia in NH with infarction |
| 3 | PTC AC due to thick colloid Suspicious for PTC | Follicular adenoma Follicular adenoma Follicular adenoma |

AC, atypical cytology; NG, nuclear grooves; PTC, papillary thyroid carcinoma; NH, nodular hyperplasia; HC, Hurthle cell.

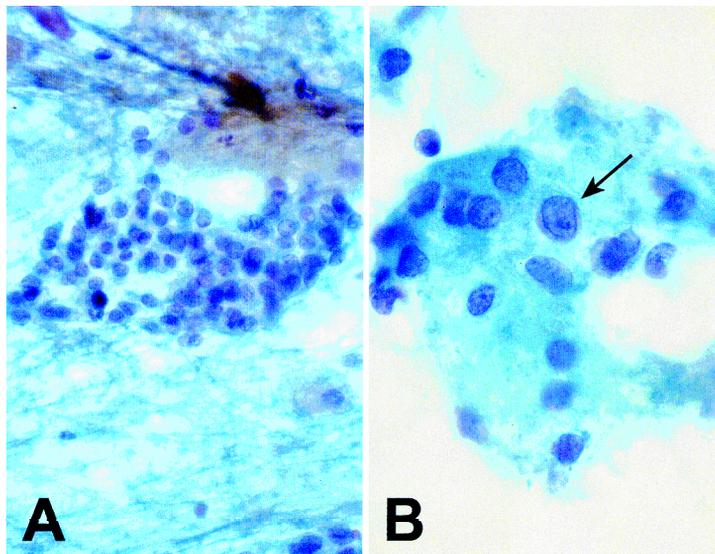


FIG. 3. Nuclear grooves, a rare feature of the follicular variant of papillary thyroid carcinoma, as a cause of a false negative finding. **A:** Most of the aspirate showed follicles with small round nuclei (400×, Papanicolaou stain). **B:** Rare cells show distinct nuclear grooves (arrow) but without intranuclear inclusions (1000×, Papanicolaou stain).

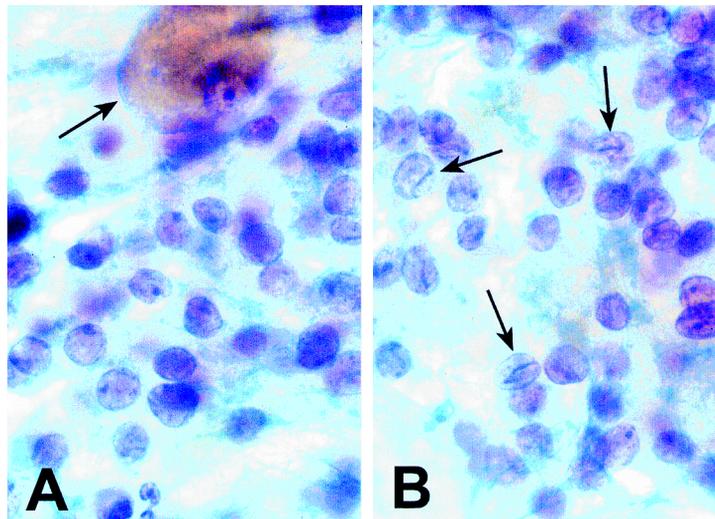


FIG. 4. Nuclear grooves, a non-specific feature, as a cause of false positive finding in a case of nodular hyperplasia, but also seen in Hashimoto's thyroiditis, follicular adenoma, and Hürthle cell adenomas. **A:** Note presence of a macrophage (arrow) in a case of a hyperplastic nodule (1000×, Papanicolaou stain). **B:** An abundance of nuclear grooves in the aspirate (arrows) (1000×, Papanicolaou stain).

TABLE 4. COMPARISON OF THE DISCREPANCY RATES OF FNA OF THE THYROID

| Author (Ref) | Year | Total thyroid FNA n | Total with surgical F/U n (%) | Study period (years) | Unsat rate % | Discrepancy rate % | False positive % | False negative % |
|----------------|---------|---------------------|-------------------------------|----------------------|--------------|--------------------|------------------|------------------|
| Current study | present | 1253 | 255 (20) | 4 | 7.8 | 18 | 6 | 4 |
| Mitra (15) | 2002 | N/R | 100 | N/R | N/R | 25 | 5-6 | 1-17 |
| Yang (20) | 2001 | 1135 | 175 (15) | 4 | 0.7 | N/R | 10 | 0 |
| Settakorn (16) | 2001 | 1761 | 415 (24) | 4 | 22 | N/R | 16.7 | 6.3 |
| Cappel (17) | 2001 | 1020 | 231 (23) | 10 | 20 | 2 | 20 | 1 |
| Bakhos (21) | 2000 | N/R | 625 | 13 | 7 | 12 | 8 | 4 |
| Baloch (18) | 1998 | 662 | 140 (21) | 3.5 | 11 | N/R | 16 | 7.5 |
| Sidawy (19) | 1997 | N/R | 133 | 4.3 | 8.3 | 27 | 10 | <1 |
| Hall (8) | 1989 | 795 | 72 (9) | 5 | 8.3 | 20 | 17 | 3 |

FNA, fine needle aspiration; N/R, not reported; F/U, follow-up; Unsat, unsatisfactory for diagnosis.

do not consider these “incidental nodules” as true “false negative” cases, as their nature can only be proven to be “false negative” if they are truly clinically significant lesions on surgical excision (22). However, some of these “microcarcinomas” can be clinically meaningful lesions as shown by Yang and colleagues in their series (23).

Another cause of the “false negative” lesion is due to the subtle cytologic features of PTC on FNA in the setting of the follicular variant. Indeed, one of our cases, showed cytologic features which were not typical of PTC with slightly enlarged cells with rare nuclear grooves as the only findings. Thick dense colloid and macrophages were seen in the background. Baloch and associates repeated a similar experience in four of their FN cases (19). Several others have also observed that the follicular variant of PTC usually present as monolayer sheets or syncytial fragments with a paucity of the classic nuclear features of papillary carcinoma which can present as a pitfall in the cytologic evaluation of these thyroid nodules (20,24,25). Therefore, although presence of nuclear grooves can be non-specific as mentioned previously, it can be the only diagnostic clue in some cases of PTC for which the other typical cytomorphic feature of nuclear inclusions as in the follicular variant, are rarely seen or lacking altogether. These difficulties in FNA interpretation of follicular variant of PTC are not encountered to the same degree in the histopathologic diagnosis.

In our “unsatisfactory for diagnosis” category, we found four of 20 cases (25%) to be of the classic PTC and three (15%) follicular adenomas in the final histopathologic interpretation. This highlights the importance of a repeat procedure in all cases for which an “unsatisfactory for diagnosis” is rendered. When evaluated as to the causes of these unsatisfactory specimens, all cases showed only blood without follicular epithelium. Eleven of those cases were performed by clinicians, seven by radiology residents and two by cytopathologists. In the latter two cases, repeat aspirates again showed blood only. The final histopathologic finding was a 1.5 cm and a 9 cm classical PTC, respectively. Gross findings of the 9 cm mass showed a multicystic lesion with numerous papillary excrescences which were not sampled by FNA.

When a clinician is in the habit of requesting an “adequacy of sampling” in their thyroid FNAs, the unsatisfactory interpretation should not be included in the category of a “false negative” diagnosis, as it is a non-diagnosis. All of the “unsatisfactory or inadequate” samples should be re-sampled before any definitive surgery is attempted. Educating our clinical colleagues as to the proper interpretation of these results would be helpful in the final outcome.

In summary, individual group practices play a role in achieving what the appropriate rates are for their practices. We are responsible for educating our clinical colleagues in the importance of obtaining an adequate sample in any FNAs but most specially in thyroid FNAs as true evaluation of false negative rates can be achieved only after years of clinical follow-up. The FP and FN rates are actually higher than the recommended values set by the Papanicolaou Task Force on Standards of Practice, but more recently remains within range from institution to institution.

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