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Nodule Heterogeneity as Shown by Size Differences Between the Targeted Nodule and the Tumor in Thyroidectomy Specimen

A Cause for a False-Negative Diagnosis of Papillary Thyroid Carcinoma on Fine-Needle Aspiration

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BACKGROUND. Missed papillary thyroid carcinoma (PTC) diagnoses on fine-needle aspiration (FNA) can result from many causes. To the authors' knowledge, the issue of whether the detection of PTC is correlated with nodule heterogeneity has not been studied to date.

METHODS. The authors identified all thyroidectomy specimens with a diagnosis of PTC that had undergone at least 1 prior FNA in the study institution between 1998 and 2003. The tumor size at the time of the resection, the ultrasound (US)-determined nodule size, and other parameters were compared between the 2 groups in which PTC was or was not diagnosed on FNA.

RESULTS. Of a total of 89 specimens, 47 were diagnosed on FNA with an average tumor size of 1.7 cm and an US-determined nodule size of 2.1 cm (a difference of 0.4 cm). Forty-two specimens with a smaller average tumor size of 0.9 cm ($P < .0001$) and a US-determined nodule size of 2.4 cm (a difference of 1.5 cm) were missed. The differences with regard to the US-determined nodule size and tumor size between the 2 groups were significant (0.4 cm vs 1.5 cm; $P < .0001$). In the missed group, 29 specimens were found to have PTC foci that measured $\leq$1.0 cm and 26 had a reasonable size difference (RSD; defined as a PTC size outside the range of $\pm$50% of the US-determined nodule size) as the indicator of the mixed nature of nodules targeted for FNA, whereas in the diagnostic group, 9 foci measured $\leq$1.0 cm and 6 had RSD. There was no cytologic evidence with which to render a diagnosis of PTC on further review in the missed group.

CONCLUSIONS. The major reason for a missed diagnosis of PTC on FNA is because of inadequate tumor sampling due to the heterogeneity of the nodule targeted for FNA. This is illustrated by the RSD noted between the targeted nodule and the actual PTC tumor focus in the resection specimen. ***Cancer (Cancer Cytopathol)*** **2008;114:27–33.** © *2007 American Cancer Society.*

KEYWORDS: thyroid, fine-needle aspiration, papillary thyroid carcinoma, missed diagnosis, nodule heterogeneity, reasonable size difference.

Papillary thyroid carcinomas (PTC) represent 75% to 80% of all malignant thyroid neoplasms.[1] Increasing sensitivities of various diagnostic modalities, including ultrasound (US)guided-fine-needle aspiration (FNA) has made it possible to detect even the smallest of lesions. Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization (WHO) as those PTC that measure $\leq$1.0 cm in greatest dimension and are found incidentally.[1] To our knowledge, the biology of PTMC is not well understood, but several

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studies have demonstrated that a certain subset can behave aggressively, demonstrating capsular invasion and lymph node metastasis.[2–4] As a result, PTMCs should be followed and treated as classic PTC.[2–4] In patients who present with a thyroid nodule, US-guided FNA is the procedure of choice to initially characterize the lesion. It is relatively fast, cost-effective, and minimally invasive. FNA has a reported sensitivity of 65% to 95% and a specificity of 70% to 100%.[5] Discrepancies between thyroid FNA and the surgical resection diagnosis can be due to several reasons, including inadequate material for evaluation, nonrepresentative sampling, and ambiguous cytologic features. To our knowledge, the issue of whether the detection of PTC is correlated with nodule heterogeneity has not been studied to date. Herein, we analyzed the size difference between the targeted nodules and PTC foci on thyroidectomy specimens as an indicator of nodule heterogeneity to address whether this affected the diagnostic accuracy of FNA.

MATERIALS AND METHODS

A computer search for all thyroidectomy specimens that had a diagnosis of PTC from 1998 through 2003 was performed at the University of Michigan Hospital (Ann Arbor, Mich). Only those resections that had at least 1 prior FNA were included in the current study. Several characteristics of both the FNA and resection specimens were noted, including exact FNA diagnosis, whether the aspirate was attended by a pathologist to assess adequacy, size of the tumor, whether frozen section was performed at the time of resection and, if it was, whether the frozen section was positive. For the cases in which PTC was not diagnosed or suspected on FNA but was subsequently diagnosed by resection, we reviewed both the FNA and resection slides to determine the reason for the discrepancy. In addition, we determined the size of the US-targeted nodule by reviewing the US and/or clinic report.

At the study institution, the majority of thyroid aspirations are performed by clinicians and are not always attended by a pathologist. During the above time frame, the majority of aspirations were performed by a radiologist/endocrinologist with US guidance. When a pathologist was not requested to attend the aspiration, the aspirated material was submitted entirely into CytoLyt (Cytyc Corporation, Boxborough, Mass). This was then centrifuged and resuspended in PreservCyt solution (Cytyc Corporation) and from this, a ThinPrep (Cytyc Corporation) slide was generated according to the manufacturer's directions. In addition, a cell block was also made. When a pathologist was requested to assess adequacy, onsite air-dried slides stained with Diff-Quik (Dade Behring, Newark, Del) were made as well as alcohol-fixed slides for Papanicolaou staining; both were referred to as conventional smears (CS). A ThinPrep slide (TP) was also made from the needle rinse and occasionally an additional cell block slide (CB) was created when there was sufficient material.

The correlation between the size of the PTC at the time of resection and the diagnostic ability of FNA was explored using standard logistic regression. The log odds of a PTC diagnosis were modeled with PTC size separately as a continuous covariate and as indicators for size categories. The size cutpoints for categories were chosen based on expert opinion, the WHO definition of PTMC, and the observed pattern of the diagnostic ability of FNA by millimeter size intervals in our cohort. The odds ratio and the probability of a correct diagnosis for each size category were calculated. When comparing covariates between groups (diagnostic vs missed), the Student 2-tailed t test and chi-square statistic were used for continuous and categoric data, respectively. For all statistical tests, P values $\leq$5% were considered significant.

RESULTS

A total of 107 FNA specimens with a histologic diagnosis of PTC, regardless of tumor size, were identified during the 6-year period. Thirteen patients underwent 2 FNAs before thyroidectomy; only the last FNA was used in the final analysis so the thyroidectomy was correlated with only 1 FNA. Five patients had PTC foci that were histologically documented as "multifocal." On US, these individual nodules were found to range from 1.5 cm to 6.0 cm. For the summary of tumor size, these 5 "multifocal" cases were excluded, resulting in a cohort of 89 cases; however, for statistical modeling purposes, these 5 cases were considered to be in the largest size group (therefore, N = 94). The female-to-male ratio was 3:1 and the average age of the patients was 43.9 years (41.6 years in women and 51.5 years in men). Forty-seven of the 89 cases were diagnosed as PTC or suspicious for PTC on FNA (sensitivity of 53%) with concordance at resection (diagnostic group). The remaining 42 cases were not diagnosed as PTC on FNA but were found to contain a PTC focus at the time of resection (missed group). Overall, 38 FNAs resulted in resections that demonstrated PTC foci that measured $\leq$1.0 cm. Of these, 29 (76%) were missed by FNA. Table 1 summarizes the characteristics of the 2 groups. Finally, 4 cases had a cystic

TABLE 1
Comparison Between the 2 FNA Groups in the Cohort (N = 89)

		Diagnostic group	Missed group
ALL	No.	47 FNAs	42 FNAs
	Average tumor size (range), cm	1.7 (0.6–4.0)*,†	0.9 (0.05–3.5)*,‡
	Pathologist assessing adequacy	32	26
	Average no. of passes	5	6
	Frozen section performed	10	14
	Confirmed PTC?	6	7
	Multifocal	3	2
	Double FNAs	6	7
	Reasonable size difference	6	26
	Average US nodule size, cm	2.1†	2.4‡
≤1.0 cm	No.	9	29
	Average tumor size (range), cm	0.9 (0.6–1.0)	0.4 (0.05–1.0)
	Pathologist assessing adequacy	7	20
	Average no. of passes	5	6
	Frozen section performed	4	7
	Confirmed PTC?	2	2
	Double FNAs	1	4
	Reasonable size difference	0	25
>1.0 cm	No.	38	13
	Average tumor size (range), cm	1.9 (1.1–4.0)	2.2 (1.2–3.5)
	Pathologist assessing adequacy	25	6
	Average no. of passes	5	5
	Frozen section performed	6	7
	Confirmed PTC?	4	5
	Double FNAs	5	3
	Reasonable size difference	6	1

FNA indicates fine-needle aspiration; PTC, papillary thyroid carcinoma; US, ultrasound.
* Diagnostic group vs nondiagnostic group: $P < .0001$.
† Average tumor size vs average US nodule size (diagnostic group): $P = .0005$.
‡ Average tumor size vs average US nodule size (missed group): $P < .0001$.

PTC that measured >1.0 cm (2 cases had a PTC that measured 3.0 cm) at the time of resection; only 1 was diagnosed as "possibly cystic PTC" on FNA and the others were considered "cystic content."

In the diagnostic group, the size of the nodules targeted by US imaging for FNA averaged 2.1 cm (range, 0.8–5.0 cm). On resection, the average PTC size in the diagnostic group was found to be 1.7 cm. The absolute difference between the US size and the resection size was 0.409 cm, a difference that was statistically significant ($P = .0005$). Thirty-eight thyroidectomy specimens had a tumor size >1.0 cm whereas 9 specimens had a tumor size of ≤1.0 cm. Comparing the cytologic features of tumor cells from the aspirates of both large (>1.0 cm) and small (≤1.0 cm) nodules, no definitive differences could be appreciated. In the diagnostic group, 6 patients had undergone 2 prior FNAs. The findings of the first FNA in this 6-case set were nondiagnostic (3 cases), multinodular hyperplasia (1 case), lymphocytic thyroiditis (1 case), and atypical follicular epithelium (1 case), whereas the second (repeat) FNA did reveal PTC in all 6 patients. Thirty-two of the total 47 FNAs (68%) in the diagnostic group were performed with a pathologist assessing adequacy, resulting in an average of 5 passes per procedure and cytologic evaluation on CS and TP (and CB) slides. Of these 32 cases, 9 (28%) were diagnosed as suspicious for PTC. Conversely, of 15 cases not attended by a pathologist (resulting in morphology evaluation on TP and CB slides only), 9 (60%) were termed suspicious for PTC. In the diagnostic group, 10 cases had frozen sections performed; 6 were correctly diagnosed as PTC. The 4 missed cases were the result of interpretation difficulties encountered on frozen section because 1 was the follicular variant of PTC, another was the sclerosing variant of PTC, and 2 had a background of florid lymphocytic (Hashimoto) thyroiditis.

In the missed group, the size of the nodules targeted by US for FNA averaged 2.4 cm (range, 0.6–5.0 cm), a finding that was not statistically significantly different from the diagnostic groups ($P = .1912$). At resection, the average PTC size in this group was found to be 0.9 cm, which is much smaller than that of the diagnostic group (1.7 cm) ($P < .0001$). The difference between the US size and the resection size was 1.451 cm, a difference that also was statistically significant ($P < .0001$). Thirteen cases had a tumor size >1.0 cm and the remaining 29 cases measured ≤1.0 cm. In this group, 7 patients had undergone 2 prior FNAs. Neither of the FNAs was diagnostic of or suspicious for PTC and was termed nondiagnostic (1 case), atypical follicular cells (1 case), Hurthle cell neoplasm (1 case), nodular hyperplasia (2 cases), and follicular lesions (2 cases) in both aspirates. Similar to the diagnostic group, 26 of the total 42 FNAs (62%) in the missed group were performed with a pathologist assessing adequacy, resulting in an average of 6 passes per procedure. Fourteen cases had frozen sections performed; 7 were correctly diagnosed as PTC, only 2 of which measured ≤1.0 cm. All 7 cases that were missed on frozen section had small PTC foci, most of which measured <0.5 cm, with a background of large, multinodular goiter nodules making them difficult to identify. Table 2 summarizes the FNA diagnoses in the missed group. Further cytologic review of these cases confirmed the original diagnoses, which included nodular hyperplasia, lymphocytic thyroiditis, and follicular cell lesion, and there were no cytologic features to suggest a diagnosis of PTC.

To better evaluate whether the heterogeneous nature of the nodule, as indicated by the size difference between FNA US-targeted thyroid nodules and actual PTC foci, contributed to the missed PTC diag-

nosis on FNA, we arbitrarily defined "reasonable size difference" (RSD) as the PTC focus in the resection specimen being outside of ± 50% of the US-determined or clinically determined nodule size. For example, an FNA was diagnosed as nodular hyperplasia and at resection demonstrated a PTC focus measuring 0.1 cm; the US size of the target nodule was 3.1 cm. According to the above definition, this is an RSD. Of the 42 specimens in the missed group, 26 (62%) fell within our definition of RSD, essentially meaning that the FNA-targeted nodule was heterogeneous in nature and much larger than the PTC focus identified at the time of resection (Fig. 1). Of these 26 specimens, 25 demonstrated PTC foci that measured ≤1.0 cm. For the remaining 16 specimens in which there was no RSD, 6 were inadequate and the remaining cases were interpreted as Hurthle cell lesions (2 cases), follicular lesions (3 cases), nodular hyperplasia (4 cases), or Hashimoto thyroiditis (1 case). If the RSD nodules and inadequate FNAs from the missed group are not considered, then the diagnostic sensitivity increases to 82% from 53%. Of the 47 specimens in the diagnostic group, only 6 (13%) had an RSD whereas the remaining 41 specimens did not (Fig. 2). For 9 PTCs in the diagnostic group measuring <1.0 cm, no RSD was demonstrated. Furthermore, when comparing the differences between the average tumor size at resection and the average US-determined nodule size between the missed group (1.451 cm) and diagnostic group (0.409 cm), the difference was also statistically significant ($P < .0001$) (ie, there was a difference between the differences).

When examining the actual proportion of correct diagnoses by tumor size interval using all 94 FNA specimens, there appeared to be a steady increase in the proportion of correctly diagnosed FNAs, then a plateau, and then a decrease as the size became >2.5 cm (Fig. 3). Visually, there appeared to be breakpoints at 1.0 cm and 2.5 cm. The odds of a correct PTC diagnosis using these breakpoints separate the tumor size into 3 groups: ≤1.0 cm, 1.0 cm to 2.5 cm, and ≥2.5 cm. If we use the group of tumors measuring 1.0 cm to 2.5 cm as a reference, the odds of an incorrect diagnosis are increased 12 times (odds ratio [OR] of 12.0; 95% confidence interval [95% CI], 4.2 – 34.4 [P < .0001]) for smaller tumors and are increased 4 times (OR of 4.1; 95% CI, 1.1–15.2 [$P = .0329$]) for larger tumors. A statistical model with the tumor size divided into groups of ≤1 cm, 1.0 cm to 2.5 cm, and ≥2.5 cm demonstrates the probability of a correct FNA diagnosis of PTC at 19.51%, 78.57%, and 50%, respectively.

TABLE 2
Distribution of the FNA Diagnosis in The Missed Group

Multinodular hyperplasia	21
Hashimoto thyroiditis	3
Hurthle cell neoplasm	2
Hurthle cell lesion	1
Follicular neoplasm	1
Rare atypical cells	1
Nondiagnostic	13
Total	42

FNA indicates fine–needle aspiration.

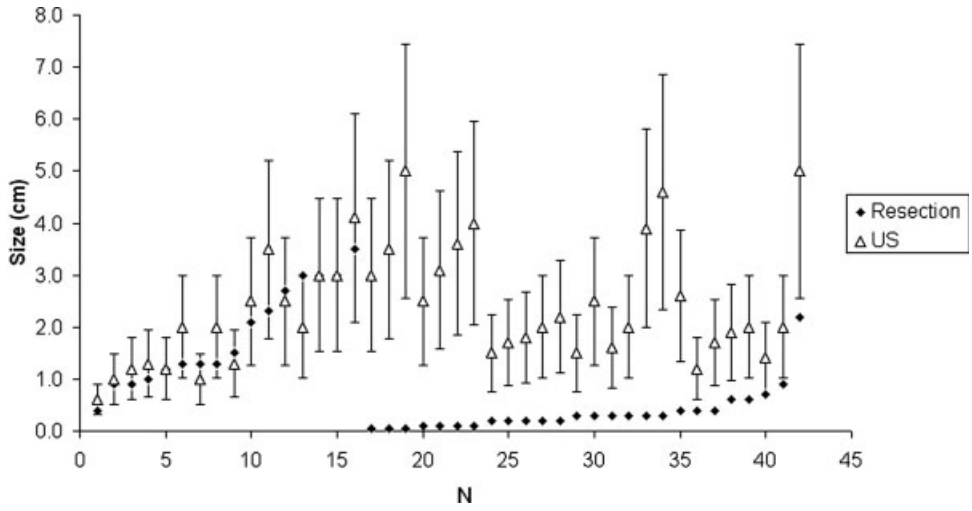

FIGURE 1. Comparison of ultrasound (US)-determined nodule size (open triangle) with ±50% range and tumor size at the time of resection (filled diamond) for each thyroidectomy specimen in the fine-needle aspiration missed group (the x axis lists each case, numbered N1−N42).

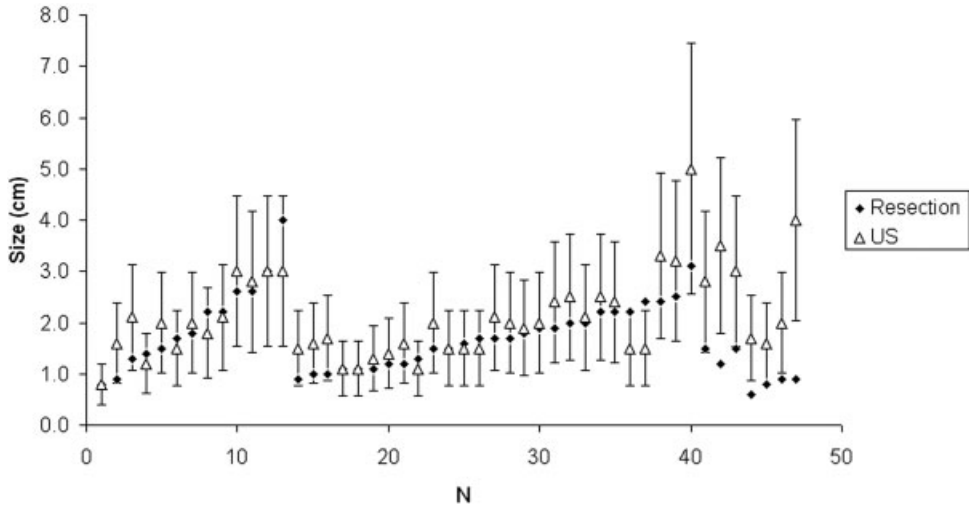

FIGURE 2. Comparison of ultrasound (US)-determined nodule size (open triangle) with ±50% range and tumor size at the time of resection (filled diamond) for each thyroidectomy specimen in the fine-needle aspiration diagnosed group (the x axis lists each case, numbered N1−N47).

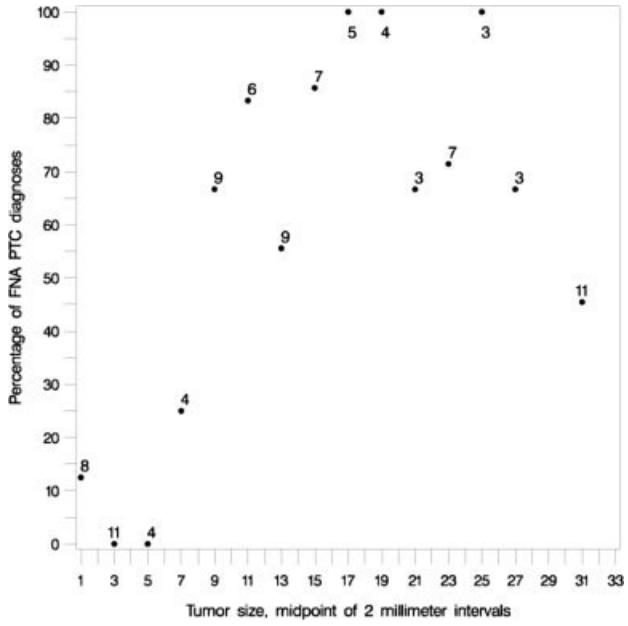

FIGURE 3. Actual percentage of correctly diagnosed cases plotted at the midpoint of 2-millimeter intervals for the size of the final resected tumor. The frequency of cases was indicated for each interval. FNA indicates fine-needle aspiration; PTC, papillary thyroid carcinoma.

DISCUSSION

The use of highly sensitive US-guided FNA of the thyroid has greatly enhanced our ability to detect and diagnose thyroid pathology without the need for more invasive procedures. However, a recent publication demonstrated that the concordance in nodules measured by US and surgical pathology examination is ≤50% in the majority of cases.[6] When US-guided FNA is employed for nonpalpable thyroid nodules (≤1.0 cm), most institutions report adequate aspirations.[7] The characterization of thyroid nodules by US is possible and routinely performed. Features such as microcalcifications, irregular surgical margins, and marked hypoechogenicity suggest malignancy and warrant an FNA.[8] In addition, nodules that are clinically worrisome demonstrate rapid growth, contain a dominant nodule among uniformly smaller nodules, have concurrent palpable or sonographically documented abnormal cervical lymph nodes, or are recurrent cystic nodules.[9] Even with these clinical and sonographic features, it is still possible to not adequately sample a small PTC focus. Specifically, if the targeted nodule is relatively large and heterogeneous with non-PTC components, the small PTC focus may not be sampled, even with an "adequately sampled specimen." Our goal herein was to determine whether the heterogenetic nature of the nodule contributes to missing the diagnosis of PTC, including PTMC, on an FNA when the resection does indeed contain PTC.

In the current study, we demonstrated that, on resection, PTCs in the FNA diagnostic group were significantly larger than in the FNA missed group (1.7 cm vs 0.9 cm; $P < .0001$). We further demonstrated that the US-targeted nodules were larger than the eventual PTC foci in both the diagnostic and missed groups but were more significant in the missed groups (size difference of 0.4 cm vs 1.5 cm; $P < .0001$). Because there was a significant size discrepancy between the targeted nodules and the actual tumor foci, indicative of the heterogeneous nature of the target nodule, the missed PTC diagno-

sis was most likely due to inadequate sampling of tumor cells on FNA because no features of PTC were noted on those FNA specimens. Therefore, they were missed not because of interpretation error but because tumor cells were not sampled, although most specimens were deemed adequate for evaluation. The average number of passes and onsite evaluation did not appear to have any noticeable impact on the ability to make the diagnosis of PTC because there was no difference noted between the diagnostic and missed groups with regard to these aspects. Although FNA operator experience has been demonstrated to affect diagnostic yield by others,[10] we did not address this issue in the current study. We considered it not to be a major factor affecting the FNA diagnosis because at the study institution, the majority of cases were performed or supervised by an experienced endocrinologist or radiologist; we regarded all of them to be at a similar experience level.

In the missed group, 26 of 42 nodules were within our definition of RSD. In other words, the PTC focus in the resection specimen and the target nodule in the US study were significantly different with regard to their sizes, which is indicative of the heterogeneous nature of the targeted nodules. In striking contrast, 87% of the specimens in the diagnostic group (100% of those with a PTC focus $\leq$1.0 cm) demonstrated no RSD and therefore the target nodule at FNA and the PTC focus identified at the time of resection are presumed to be one and the same. The correlation between the mixed nature of the nodule and PTC diagnostic accuracy is made even clearer because 25 of 26 nodules in the missed group measured $\leq$1.0 cm (PTMC). Because nodules measuring <1.0 cm on US are often not being subjected to FNA, PTMC would often be found in target nodules measuring >1.0 cm, thus generating potential RSD and no sampling of the tumor on FNA. This would result in a low diagnostic yield on FNA, which is supported by our statistical model as shown in Figure 3, with a 19.51% probability of diagnosing PTC when the PTC foci measures <1.0 cm. When PTCs are in the range of 1.0 cm through 2.5 cm, a much better diagnostic yield (78.57%) is achieved because those nodules appear to be more homogeneous, with a similar size in the targeted nodule and the tumor.

PTMC, for the most part, is clinically insignificant because it has been found in approximately 33% of autopsy or unexpected surgical cases.[3] However, there is a small percentage of these that do behave more aggressively and demonstrate capsular invasion and lymph node metastasis.[1,3] Distinguishing PTMC from ordinary PTC on FNA is virtually impossible. Perez et al. described 8 cases of thyroid FNAs that were suspicious for PTC and were found on histologic examination to be PTMC.[11] On histologic examination, each of these specimens contained a focus of PTMC ranging from 0.1 cm to 0.4 cm that was adjacent to the larger non-PTC nodules that were targeted for FNA. In our study, the average size of PTC foci in the missed (false-negative) group was 0.9 cm and, overall, 38 patients had PTC that by definition was PTMC. We considered this to be the main reason why, in our cohort, the sensitivity of the FNA diagnosis of PTC is lower than that in the literature.[5] When we examined frozen sections performed on thyroidectomy specimens based on tumor size (Table 1), tumors that measured $\leq$1.0 cm were more likely to be missed because small PTC foci were masked by the background of larger benign nodules/lesions. This brings credence to the notion that the mixed nature of the nodule is an important factor in the false-negative diagnosis of PTC on FNA.

In a College of American Pathology Laboratory Improvement Program, those FNA specimens that lacked marked nuclear enlargement, chromatin clearing, and intranuclear inclusions were more likely to be misdiagnosed as something other than PTC.[12] Cases that performed well included those that had the typical features of PTC. In the current study, the cases in the missed group did not have features that would have raised the suspicion for PTC. Therefore, misinterpretation was not the reason a diagnosis was not made.

Although the TP has demonstrated diagnostic sensitivity and specificity similar to those of CS,[13,14] Michael and Hunter have shown potential pitfalls that are unique to this process.[15] In our study, although the TP-only and CB-only specimens in the diagnostic or missed groups were similar, not generating bias for diagnosis, the above mentioned pitfalls were noted. In the diagnostic group, those pitfalls might also have contributed to a diagnosis of "suspicious for PTC" in 9 of 15 cases (60%) evaluated with TP and CB only, a finding that is much higher than that of cases with onsite assessment and evaluated by a combination of CS and TP and/or CB (28%). Therefore, it is logical to conclude that the combination of the onsite adequacy assessment and cytologic evaluation CS reduced the number of cases with a suspicious diagnosis, although the current study was not designed to compare these 2 preparation methods.

Cystic masses pose an additional diagnostic challenge that has been well documented.[16,17,18] Cystic masses contribute to interpretation errors with

"atypical" cells.[16] In addition, a cystic mass also generates RSD, an indicator of nodule heterogeneity, thus affecting tumor sampling. In Figure 3, at the 2.5-cm cutoff point, there was a counterintuitive decrease in the probability of a correct diagnosis to 50%. This is in part because of the finding that 2 cases in this group were diagnosed as "cyst contents" on FNA but subsequently were found to demonstrate cystic PTC (3.0 cm) at the time of surgical resection because thyroid lobectomy is advocated for large cystic lesions.[17,18] In addition, 2 missed cases with multifocal but small PTC foci that might be more difficult to sample were included in this >2.5-cm group.

In conclusion, the major reason for a false-negative diagnosis of PTC on FNA is because of inadequate tumor sampling due to the mixed nature of the lesion/heterogeneity of the nodule. This is illustrated by the RSD between the targeted nodule and the actual PTC tumor focus in the resection specimen.

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