Sonographically Guided Fine Needle Aspiration of Thyroid Nodule: Discrepancies between Cytologic and Histopathologic Findings

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Received 22 June 2006; accepted 18 June 2007

ABSTRACT: Purpose. To analyze the discrepancies between the cytologic results of sonographically (US)-guided fine needle aspiration (FNA) of thyroid nodules and final histopathologic results and to discuss the limitations of US-guided FNA.

Materials and Methods. The results of US-guided FNAs performed by a single experienced radiologist in 315 thyroid nodules in 292 patients (246 women, 46 men aged 12–79 years) were retrospectively correlated with their surgical pathologic results. The FNA results were classified as nondiagnostic, indeterminate, negative, or positive, whereas final pathologic diagnoses were classified as malignant or benign.

Results. The FNA results were nondiagnostic in 31 cases (9.8%), indeterminate in 97 cases (30.8%), and determinate in 187 cases (59.4%). Of the 187 conclusive cases, 169 (90.4%) were concordant with the final pathologic results, whereas 18 (9.6%) were discordant with 14 false-positive and 4 false-negative results. These discrepancies were caused by atypical nuclear features. Among the 97 indeterminate and 31 nondiagnostic cases, a malignancy was found in 14 (14.4%) and 8 (25.8%) cases, respectively. In addition, 10 papillary carcinomas, which were not visualized on sonograms, were detected incidentally in thyroidectomy specimens.

Conclusion. The diagnostic accuracy of US-guided FNA of thyroid nodule has limitations that should be minimized by careful interpretation of the cytologic findings and accurate sampling. DOI: 10.1002/jcu.20412 Keywords: fine needle aspiration; thyroid; benign disease; cancer; ultrasonography

The prevalence of thyroid nodules in the general population has been reported to be 4–7% on palpation alone1 and 10–41% on sonography (US),2–4 with approximately 9.2–12.0% of the latter being malignant.5,6 To avoid inadequate sampling during fine needle aspiration (FNA), US guidance has been used increasingly to direct the fine needle into minute nonpalpable thyroid nodules or into the solid or peripheral areas of complex nodules to avoid cystic or necrotic areas, which might lead to inadequate samples.7–9 The wide use of US-guided FNA has resulted in an overall decrease in the number of thyroidectomies performed on cold nodules, with a concomitant increase in the cancer yield at surgery.7–9

Despite the increased diagnostic accuracy, US-guided FNA still has limitations, such as false-positive and false-negative results, as well as inadequate sampling.10–14 In addition, the distinction between a follicular malignancy, such as a follicular carcinoma or a follicular variant of papillary carcinoma, from benign lesions, such as a follicular adenoma or nodular adenomatous goiter, is very limited on cytologic grounds.15,16 In this study, we analyzed our results of US-guided
FNA of thyroid nodules and focused on the discrepancies between cytologic and final pathologic results.

**PATIENTS AND METHODS**

This retrospective study included 1,450 patients who underwent US-guided FNA of a thyroid nodule at our institution from February 2002 to October 2005. The patients had been referred for evaluation of thyroid nodules detected incidentally during sonographic examination of the neck (eg, carotid sonographic examination) at our and other institutions. Additionally, patients with nondiagnostic palpation-guided FNA were included. None of the patients had undergone radiotherapy of the head or neck. Of these 1,450 patients, we identified 292 (246 women and 46 men) consecutive patients who subsequently underwent a hemi- or total thyroidectomy. The mean age of the patients at the time of operation was 47.7 ± 13.4 years (range, 12–79 years). In the 292 patients, 315 thyroid nodules, ranging in size from 0.4 to 5.5 cm (mean ± SD size: 2.2 ± 0.7 cm), were sampled preoperatively using US-guided FNA. At surgical pathology, there were 143 cancers (45.4%), including 134 papillary, 4 Hurthle cell, 2 follicular, 2 medullary, and 1 anaplastic.

**US-Guided FNA**

US-guided FNA was performed on solitary or multiple thyroid nodules by a single board-certified radiologist using a 22-gauge needle attached to a 10-ml syringe, with 2–4 passes through the target lesion. HDI 5000 iU-22 scanners (Philips Medical Systems, Bothell, WA) and a Sonoline Antares scanner (Siemens Ultrasound, Mountain View, CA) were used for guidance with broadband high-frequency (7–15 MHz) linear transducers. The sonographic characteristics of the lesion were assessed. The malignant sonographic characteristics included marked hypoechogenicity, irregular or microlobulated margin, and presence of internal microcalcifications. Microcalcifications appeared as tiny, punctate hyperechoic foci. The nodule was classified as a malignancy if at least 1 malignant sonographic finding was identified, and FNA was performed regardless of the size.

During real-time US visualization, the entire length of the needle was seen until it reached the thyroid nodule (Figure 1). The needle was then moved back and forth with minimal suction pressure. The specimens were smeared on slides, fixed immediately in 95% ethanol, and stained using the Papanicolaou method. The smears were not assessed immediately by a cytopathologist.

**Cytologic Interpretation, Correlation with Surgical Pathology, and Statistical Analysis**

According to the guidelines published by the Papanicolaou Society, a sample was considered adequate if there were more than 6 well-visualized, well-preserved groups of follicular epithelium, with each group containing at least 10 cells. All specimens were interpreted by experienced staff cytopathologists. All aspirates were categorized as being nondiagnostic (inadequate sampling), indeterminate, negative, or positive for malignancy. To distinguish a follicular carcinoma from other benign conditions, capsular or vascular invasion must be thoroughly searched for on multiple permanent sections after a complete surgical excision. Because such invasion cannot be diagnosed with FNA, aspirates showing follicular or Hurthle cell neoplasm were considered indeterminate for a malignancy. After surgery, all the final histopathologic diagnoses of thyroid nodules were categorized as benign (including nodular hyperplasia, follicular or Hurthle cell adenoma, and Hashimoto’s thyroiditis) or malignant (including papillary, medullary, anaplastic, follicular, and Hurthle cell carcinomas).

Correlation was made between cytologic and surgical pathologic diagnoses after surgical resection, and discordant results were specifically reviewed. We calculated overall sensitivity, specificity, false-positive, and false-negative rates of US-guided FNA in the diagnosis of thyroid malignancy after exclusion of the indeterminate and nondiagnostic aspirates.
RESULTS

Overall Cyto-histopathologic Analyses of US-Guided FNA for Thyroid Nodule

The FNA results of the 315 thyroid nodules were diagnostic in 284 cases (90.2%) and nondiagnostic in 31 cases (9.8%). Diagnostic aspirates were indeterminate in 97 cases (34.2%), positive for malignancy in 121 cases, and negative for malignancy in 66 cases. The results of 315 FNAs are shown in Figure 2.

Of the 187 nodules with conclusive cytologic results, correlation with surgical pathology showed concordance in 169 (90.4%) and discordance in the remaining 18 (9.6%), with 4 false-negative and 14 false-positive results (Table 1). Based only on cases with conclusive cytologic results, the overall sensitivity and specificity of US-guided FNA in the diagnosis of thyroid malignancy were 96.4% (107/111) and 81.6% (62/76), respectively.

Discrepancy between Cytology and Surgical Pathology

All 4 false-negative FNA results occurred in cases of papillary carcinoma. A review of these cases showed that the 4 pathologically proven papillary carcinomas had been cytologically misinterpreted as being negative for a malignancy because they did not exhibit the classic nuclear features of a papillary carcinoma.

False-positive results were obtained in 14 nodules, which were interpreted as being positive for a malignancy, but surgical pathology was benign. The final pathologic diagnoses were nodular hyperplasia (8 cases), follicular adenoma (4 cases), Hurthle cell adenoma (1 case), and Hashimoto’s thyroiditis (1 case). In those cases, atypical nuclear features, including a nuclear groove and/or nuclear inclusion, mimicked a malignancy. In 1 case of nodular hyperplasia and case of follicular adenoma, papillary formations were also noted on the aspirates.

The 97 nodules with indeterminate FNA results corresponded pathologically with 14 (14.4%) thyroid malignancies, including 9 papillary carcinomas, 2 follicular carcinomas, 3 Hurthle cell carcinomas, and 83 (85.6%) benign lesions, including 63 nodular hyperplasias, 19 follicular adenomas, and 1 Hurthle cell adenoma. Review of the 14 cases with indeterminate cytologic results showed...
logic results, which were subsequently confirmed to be malignant on pathologic examination, revealed that the causes of the missed diagnosis of malignancy were atypical nuclear features in 9 cases and overlapping cytologic features in 5 cases. Moreover, preoperative cytologic evaluation alone did not distinguish carcinoma from adenoma in cases with 3 Hurthle cell carcinomas and 2 follicular carcinomas. In addition, 10 papillary carcinomas <0.5 cm in diameter were incidentally found adjacent to benign follicular neoplasms.

Nondiagnostic aspirates were obtained in 31 nodules (9.8%). Of these, 8 (25.8%) were found to be malignant (8 papillary carcinomas) and 23 (74.2%) were benign (17 nodular hyperplasias, 5 follicular adenomas, and 1 Hurthle cell adenoma) on the final pathology tests. A review of these cases confirmed all the nondiagnostic aspirates, including the 8 histopathologically verified papillary carcinomas, were suboptimal because of the paucity of follicular cells that were diluted with blood or colloid. Of these 31 initially nondiagnostic aspirates, repeat US-guided FNA provided adequate samples in 9 of 10 cases with a diagnosis of malignancy in 3 cases pathologically confirmed as malignant. The other 21 nodules with nondiagnostic FNA results were surgically resected without repeat aspiration.

DISCUSSION

Most papillary and medullary carcinomas of the thyroid can be diagnosed with FNA with a high sensitivity and specificity. However, false-positive, false-negative, and nondiagnostic results do occur due to the nature of the lesions and, in most instances, insufficient experience of the radiologist or cytopathologist. In addition, FNA can be limited in the case of follicular neoplasm.

The false-positive rate was 11.6% (14/121) in our study. This is slightly higher than other recently reported false-positive rates ranging from 4% to 8%. The main reason for this higher false-positive rate is attributed to the presence of several morphologic features mimicking papillary carcinoma such as intranuclear inclusions, nuclear groove, papillary architecture, and concomitant absence of colloid in the aspirates. These features can be seen in aspirates from Hashimoto's thyroiditis, nodular hyperplasia, follicular adenoma, and Hurthle cell adenoma.

The 6.1% false-negative rate for malignancy in our study was similar to that reported in the literature (2–7%) and is generally attributed to cytologic misdiagnoses, often in the setting of a follicular variant of a papillary carcinoma. Cytologic diagnosis of this entity can be difficult due to the paucity of nuclear features of papillary carcinomas and the overlapping features with other follicular neoplasms.

Indeterminate cytologic results occurred in 30.8% of cases in our study versus the 42% reported in the literature. This category is largely composed of follicular neoplasms, which show a pattern of microfollicles, high cellularity, and scant colloid. Because these cytologic findings occurred in a follicular adenoma, follicular carcinoma, nodular hyperplasia, and follicular variant of a papillary carcinoma, it is not possible to clearly differentiate them cytologically, and a surgical excision is recommended for a definite pathologic diagnosis.

In our study, 14 (14.4%) of the 97 US-guided FNAs whose results were described as follicular or Hurthle cell neoplasms were pathologically malignant on permanent section. This is similar to the estimated 10–20% malignancy rate in indeterminate thyroid aspirates reported in the literature. In an attempt to avoid unnecessary surgery of thyroid nodules with follicular neoplasm, some authors have further stratified the indeterminate thyroid aspirates into high- and low-risk groups for a malignancy based on clinical parameters. Baloch et al reported male sex, age >40 years, and a nodule size >3 cm to be significantly associated with a higher likelihood of malignancy. Similarly, Davis et al added a history of neck irradiation to those parameters associated with a risk of malignancy, including size >3 cm and age >50 years; however, sex and family history of goiter or neoplasm were not pre-disposing factors. On the other hand, McHenry et al reported that these clinical factors were not helpful in predicting a carcinoma in patients with a follicular neoplasm. With respect to the cytologic features, cellular atypia has been found to be associated with a higher risk of malignancy by some investigators but not others. Markers of a malignancy—in particular HBME-1, galectin-3, and Ret proto-oncogene—even in a small thyrocyte population, may improve the diagnostic accuracy of FNA of thyroid nodules in the future.

Despite the improved aspiration technique and US guidance, up to 20% of initial aspirations are nondiagnostic. The highest proportion of nondiagnostic specimens occur in nodules with a large cystic content, and malignancy has been observed in 5–10% of cases with nondiagnostic
aspirates.\textsuperscript{31–33} Therefore, repeated US-guided FNA should be performed in cases of nondiagnostic nodules aspirates. In our series, we obtained a diagnostic specimen after repeating the FNA in 9 of 10 cases (90\%) of initially nondiagnostic FNA, with 3 cases being positive for malignancy. Other factors have been reported to have an impact on the success of FNA, including small size of the nodule (eg, <5 mm), location of the nodule within the thyroid, and presence of calcification.\textsuperscript{8,34}

Because our results were obtained exclusively from patients undergoing thyroid surgery, they must be interpreted with caution before being applied to the general population of patients with thyroid nodules. Our malignant yield of 42.2\% after a surgical resection was higher than the reported incidence of 9.2–12.0\% of thyroid cancer after a surgical resection was higher than the general population.\textsuperscript{5,6} Therefore, the risk of a false-negative result of US-guided FNA in the diagnosis of malignancy in our surgical series is significantly higher than what should be expected in the general population.

In conclusion, although US guidance has improved the diagnostic accuracy of FNA of thyroid nodules, FNA remains limited by nondiagnostic aspirates and indeterminate cytologic findings. A repeat US-guided FNA is a simple and effective means of improving the diagnostic yield of FNA for an initially nondiagnostic aspirate. Because US-guided FNA will undoubtedly continue to be used in the primary evaluation of thyroid nodules, awareness of its limitations is important.

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