Should “Indeterminate” Diagnoses Be Used for Thyroid Fine-Needle Aspirates of Nodules Smaller Than 1 cm?

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Fine-needle aspiration is an excellent test for the evaluation of thyroid nodules. The recent Bethesda System for Reporting Thyroid Cytopathology has met with widespread acceptance as a way to interpret these aspirates. Nevertheless, many authors believe that the indeterminate category (especially atypical follicular cells of undetermined significance, but also including suspicious for a follicular/Hürthle cell neoplasm) is overused. Indeed, ancillary testing for this group of cases is currently being suggested by some authors specifically because the risk of malignancy for patients with this diagnosis is so low. It would seem that any suggestion that could help reduce the rate of indeterminate diagnoses without lowering the sensitivity would be of benefit, and a variety of suggestions have been made.

We have noted in our practice that in some cases clinicians will aspirate nodules that are smaller than 1 cm, and some of these cases are given indeterminate diagnoses. Although we have identified malignancies in this group of patients, we have noted that they are almost always papillary carcinomas, regardless of the subclassification given to the case. We also noted that approximately 10% of these and our benign cases have incidental papillary carcinomas at the time of resection. Given this, we wondered if the rate of detection of papillary carcinomas smaller than 1 cm was any higher in these indeterminate cases than in cases without an indeterminate diagnosis. To assess this, we correlated our results of thyroid aspiration with resection during the last 16 years.

METHODS

All thyroid fine-needle aspirates interpreted at our hospitals from the 16-year period October 1996 through June 2012 were reviewed and the results correlated with the results of histologic follow-up.

For this study cases were reclassified according to the most recent Bethesda System for Reporting Thyroid Cytopathology. Within the cases that were classified as atypical follicular cells, 4 distinct subtypes were recognized by the pathologists who diagnosed these cases. Atypical cells, rule out papillary carcinoma, had a small number of cells that had some features of papillary carcinoma. Typically these cells were rare (as few as 20 cells per case) and had focal nuclear enlargement and clearing. Inclusions were not identified. Atypical cells, rule out Hürthle cell neoplasm, had 2 different patterns that have been described previously. Either the case was almost exclusively Hürthle cells, but the number of cells was scant, or the case had numerous Hürthle cells but lacked significant atypia. Atypical cells, rule out a follicular neoplasm, had cells that were arranged in a mixed macrofollicular and microfollicular pattern, with minimal to no cytologic atypia. Atypia not...
otherwise specified was a heterogeneous group of cases that typically had rare cells with atypia that was difficult to further classify. Cases classified as suspicious for a follicular neoplasm had numerous microfollicles with cytologic atypia. Cases classified as suspicious for a Hürthle cell neoplasm had numerous Hürthle cells.

All aspirates were performed by clinicians. Approximately one-third of aspirates were performed in clinicians’ offices without imaging studies. Between 2 and 8 passes were made. Two-thirds of aspirates were performed in the radiology department, with the aid of ultrasound guidance and immediate evaluation. Direct smears were made in all cases, and all were alcohol fixed and stained with either the Papanicolaou or hematoxylin-eosin stain. If sufficient material was obtained, cell blocks were also made. Core needle biopsy was also available in approximately 400 cases. These core biopsies significantly lowered the nondiagnostic rate, but did not significantly alter the atypia rate. None of the cases smaller than 1 cm had core needle biopsies performed.

The size of the nodule was determined by gross examination at the time of resection. Incidental carcinomas were carcinomas smaller than 1 cm in greatest dimension in which features of papillary carcinoma could not be identified on the preceding aspirate.

The reason for referral of patients with a benign nodule is not known, but may be related to other clinical issues rather than to benign diagnosis on fine-needle aspiration. The rate of malignancy reported in these benign aspirates represents incidental carcinomas found in the resection specimen and not the false-negative rate of a benign diagnosis on thyroid aspiration.

Categorical analysis was done using a 2-tailed $\chi^2$ test for tests. A $P$ value of $\leq .05$ was considered significant.

**RESULTS**

During the time period, a total of 9080 cases were aspirated, and 1393 resections were performed. Of those resected, a total of 236 (17%) were classified as atypical follicular cells of undetermined significance, and 256 (18%) were classified as suspicious for a follicular/Hürthle cell neoplasm.

A total of 33 of 331 (10%) incidental papillary carcinomas (all $<1$ cm) were identified in benign aspirates with resection. The incidence in benign nodules that were aspirated and smaller than 1 cm (10 of 63; 15.8%) was not significantly different than the incidence in benign nodules larger than 1 cm (23 of 268; 8.6%; $P = .08$), and subsequently these cases were grouped together for further analysis. This was not significantly different than the 52 incidental papillary carcinomas identified in the indeterminate cases at resection (52 of 492; 11%; $P = .78$).

A total of 37 atypical follicular cells of undetermined significance cases (16%) and 21 (8%) suspicious for a follicular/Hürthle cell neoplasm cases were for nodules smaller than 1 cm in diameter; see the Table. Thirteen of these cases had the diagnosis of atypical, a papillary carcinoma cannot be ruled out, and 5 (38%) of these 13 cases had carcinoma on resection, all of which were papillary. This rate was significantly higher than the rate of papillary carcinomas smaller than 1 cm found in the rest of the indeterminate cases (6 of 45; 13%; $P = .04$). The rate of malignancy for cases diagnosed as atypical follicular cells, cannot rule out a follicular neoplasm (18%), and suspicious for a follicular neoplasm (2 of 7; 25%) together was not significantly different from that found for nonincidental (1 cm) papillary carcinomas found in the rest of the indeterminate cases (2 of 29; 7%; $P = .08$). When cases subtyped as atypical, a papillary carcinoma cannot be ruled out, were removed (13 cases), the remaining 24 and 21 aspirates identified 3 tumors each (13% and 14%), all papillary carcinomas. On review of these 6 cases, the 6 were found to have some nuclear features suggestive of papillary carcinoma (pale chromatin, nuclear grooves, irregular nuclear outline) in addition to features suggestive of either follicular or Hürthle cell neoplasms, which was why they were not classified as incidental tumors.

Together, the incidence of identified carcinomas in these 45 indeterminate cases was not significantly different than that of incidental carcinomas found in the rest of the indeterminate cases (6 of 45; 13% versus 11%; $P = .48$). The rate of identified carcinomas was significantly less than for similar indeterminate cases smaller than 1 cm (excluding cases of atypical, papillary carcinoma cannot be ruled out) (88 of 330 cases; 27%; $P = .05$).

If the indeterminate cases other than papillary carcinoma cannot be ruled out for nodules smaller than 1 cm are removed (45 cases), the overall indeterminate rate (at resection) for this series decreases 9% from 492 to 442.

**COMMENT**

The major conclusion of this article is that cytologists should not use indeterminate diagnoses for nodules smaller than 1 cm unless they have features of papillary carcinoma. In addition, in this series there was one case of medullary carcinoma that measured 0.6 cm, but the aspirate was diagnostic (data not shown). This conclusion does not mean to imply that follicular and Hürthle cell carcinomas smaller than 1 cm do not exist, nor that the cytologic features of these tumors when they are smaller than 1 cm are any
different than when they are greater than 1 cm; they do exist and they are not different. They do and they are not. However, the relative incidence of carcinomas in nodules smaller than 1 cm is so low that the risk of malignancy in this setting is no different than the risk associated with an entirely benign aspirate. For this reason, it is important for the cytologist to try to distinguish these aspirates from other aspirates with similar cytologic features that are from nodules that are larger than 1 cm. One suggestion we have put forth is the use of a “favor benign” category in which patients are treated as though they have a benign aspirate, but they are flagged in such a way that the clinician can identify them as patients who may need additional clinical follow-up.7

Given these results, one may wonder whether any nodule smaller than 1 cm should be aspirated. In general this is a question that clinicians should answer. However, our results and others show that fine-needle aspiration is sensitive for papillary and medullary carcinomas in this size range. In some cases, there may be additional clinical information, such as family history or ultrasound findings, that prompt the fine-needle aspiration. In addition, papillary carcinomas smaller than 1 cm can be associated with metastatic disease.10 Finally, the worry associated with a nodule for both the clinician and patient may in some settings be best resolved by aspiration.

The results of this study are highly dependent upon the definition of incidental papillary carcinoma. In some of our previous publications, we have used a cutoff of 3 to 4 mm, based on what the clinicians were targeting at the time of aspiration.10 However, over time we have noted that the size of incidental papillary carcinomas that were entirely missed at the time of resection could occasionally be as large as 9 mm. In some cases in this series, review of the aspirate confirmed that an aspirate that was not categorized as having features of papillary carcinoma indeed had such features when they were specifically sought. The conclusion of this finding is that when dealing with aspirates from nodules smaller than 1 cm, one must be very aggressive in searching for subtle features of papillary carcinoma.

Previous studies have documented that cases with focal features of papillary carcinoma have an elevated risk of malignancy when compared with other atypical cases.8-11,13,15 These studies have suggested that these cases belong in a separate category from other indeterminate diagnoses. The results of the current study support this contention. Unfortunately, in many if not most cytology practices, this subgroup of cases is not specifically defined within the atypical follicular cells category. This may make application of the findings in this study more difficult to apply in those settings. In addition, although these cases have been identified and written about by several different groups of investigators with very similar results, and the cytologic criteria for them are among the best defined in the atypical follicular cells group, whether this group of cases can be reproducibly identified in all practices is not known.

There are several limitations in this series. First the results are dependent on the definition of an incidental carcinoma, which has varied from series to series. Second, the size of the nodule was based on the size at resection. It is possible that the size may be different when measured by ultrasound. Third, the results in some categories are based on relatively few cases; the significance of the findings might have been different if larger series had been available. Further studies of the value of fine-needle aspiration in nodules smaller than 1 cm appear warranted.

In conclusion, we have shown that for nodules smaller than 1 cm, indeterminate aspirates without features of papillary carcinomas have the same risk of malignancy as benign aspirates. Further studies are needed to confirm that cytologists should distinguish these cases from cases with indeterminate features that measure larger than 1 cm, which may have a significantly different risk of malignancy.

References
6. Renshaw AA. Hurthle cell carcinoma is a better gold standard than Hurthle cell neoplasm for thyroid fine-needle aspirates: defining more consistent and specific cytologic criteria. Cancer Cytopathol. 2002;96(5):261–266.