Diagnostic accuracy of fine needle aspiration cytology in thyroid lesions

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Received 16 October 2011; accepted 23 January 2012
Available online 25 February 2012

Abstract  Purpose: Evaluation of accuracy of fine needle aspiration cytology (FNAC) in the diagnosis of different thyroid lesions.

Patients and methods: This is a retrospective study of 296 diagnosed cases of thyroid nodules referred to cytology unit, pathology department, NCI, who underwent FNAC for diagnosis. The results were categorized according to the recent Bethesda classification into: insufficient for diagnosis, benign, atypical follicular lesion of undetermined significance, follicular neoplasm, suspicious for malignancy, and malignant sampling. The final histologic diagnosis and/or clinico-radiologic follow-up assessment for non-neoplastic lesions were considered the gold standard.

Results: The study included 296 cases presented with thyroid nodules who underwent diagnostic thyroid FNAC. Female to male ratio was 5.2:1, and the median age was 44 years. Ninety-eight cases (33.1%) were diagnosed as benign, 40 cases (13.5%) as follicular lesion of undetermined significance, 49 cases (16.5%) as follicular neoplasm, 30 cases (10.1%) as suspicious for malignancy, 58 cases (19.5%) as malignant, and 21 cases (7.1%) as unsatisfactory. Nodular hyperplasia represented the majority of benign cases (89.8%), while papillary carcinoma was the most frequent malignant lesion (72.4%). Cytologic diagnoses were compared with their corresponding final histologic ones. FNAC achieved a sensitivity of 92.8, a specificity of 94.2%, a positive predictive value of 94.9%, a negative predictive value of 91.8%, a false positive rate of 7.2%, a false negative rate of 5.8%, and a total accuracy of 93.6%.

Conclusion: FNA cytology is a sensitive, specific, and accurate initial diagnostic test for the evaluation of patients with thyroid swellings.

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of cancer, thereby avoiding unnecessary surgery and possible injury of the recurrent laryngeal nerve, hypoparathyroidism, and thyroid hormone dependence in patients with benign thyroid nodules. However, the distinction of these benign lesions from malignant nodules cannot be based reliably on the clinical presentation alone [1].

FNAC of the thyroid gland is now a well-established, first-line diagnostic test for the evaluation of diffuse thyroid lesions as well as of thyroid nodules with the main purpose of confirming benign lesions and thereby, reducing unnecessary surgery [2].

Different imaging techniques are now used for diagnosis of thyroid nodules like radionucleotide scanning, high-resolution ultrasonography, etc. However, FNAC is still regarded as the single most accurate and cost-effective procedure, particularly if ultrasound is used as a guide for better sample collection, especially for cystic lesions [3].

Published data suggest that FNA has an overall accuracy rate around 95% in the detection of thyroid malignancy [4]. Nevertheless, like any other test, FNAC has its limitations and diagnostic pitfalls. These limitations include false negative and false positive results and a proportion of FNA results that are not obviously benign or malignant and fall into the indeterminate or suspicious group [5]. The reported pitfalls are those related to specimen adequacy, sampling techniques, the skill of the physician performing the aspiration, the experience of the pathologist interpreting the aspirate and the overlapping cytological features between some benign and malignant thyroid lesions [6].

Since it was difficult to include unsatisfactory cases as well as follicular lesions of undetermined significance under any benign or malignant cytologic categories, these cases were excluded from the calculation. Statistical analysis was done using SPSS software.

Results
We included 296 cases, 48 cases (16.2%) were males and 248 cases (83.8%) were females, with female to male ratio of 5.2:1. The age ranged from 14 to 77 years, with a median age of 44 years.

FNAC results were interpreted as benign in 98 cases (33.1%), follicular lesion of undetermined significance in 40 cases (13.5%), follicular neoplasm in 49 cases (16.5%) (Fig. 5), suspicious in 30 cases (10.1%), malignant in 58 cases...
(19.5%), and unsatisfactory in 21 cases (7.1%) (Table 1). The benign diagnoses included 88 cases (89.8%) of nodular colloid goiter, and 10 cases (10.2%) of Hashimoto’s thyroiditis. The malignant diagnoses were 42 cases (72.4%) of papillary carcinoma (Figs. 1–4), 6 cases (10.3%) of medullary carcinoma (Fig. 6), and 10 cases (17.2%) of anaplastic carcinoma.

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>98</td>
<td>33.1</td>
</tr>
<tr>
<td>Follicular lesion of US</td>
<td>40</td>
<td>13.5</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>49</td>
<td>16.5</td>
</tr>
<tr>
<td>Suspicious of malignancy</td>
<td>30</td>
<td>10.1</td>
</tr>
<tr>
<td>Malignant</td>
<td>58</td>
<td>19.5</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>21</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>296</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1  A case of papillary carcinoma showing characteristic papillary configuration (top left) (Pap. ×100). The nuclei show ground glass chromatin, intranuclear cytoplasmic inclusions (thin arrow), and characteristic clefts (thick arrow) (Pap. ×400).

Figure 2  A case of papillary carcinoma featuring syncytial arrangement of cells with prominent nuclear grooves (Pap. ×400).

Figure 3  A case of papillary carcinoma with squamous metaplastic cells (right), and its histopathologic counterpart (left), showing the same squamous metaplastic cells, together with papillary carcinoma cells (Pap. ×400).

Figure 4  A case of papillary carcinoma showing multinucleated tumor giant cell beside a syncytial arrangement of tumor cells with indistinct cell borders and ground glass nuclei (Pap. ×400).

Figure 5  A case of follicular neoplasm showing atypical follicular cells with high N/C ratio and nuclear pleomorphism, arranged in three dimensional cluster with focal attempt at acinar arrangement (arrow) (Pap. ×400).
The results of FNAC were compared with their corresponding histopathological diagnoses in all cases of follicular lesion of undetermined significance, cases of follicular neoplasm, suspicious and malignant cases, and some benign diagnosed cases upon cytopathologist request in some cases and upon surgeon’s recommendation for patient’s symptoms relieve in others. Of the 49 colloid nodular cases who underwent surgical intervention, 42 cases (85.7%) were diagnosed as nodular goiter, six cases (12.2%) as follicular adenoma, and one case (2%) as carcinoma. The remaining 39 cases who did not undergo surgery and followed clinically and radiologically for 2 years, showed no significant increase in size, ultrasonographic changes, or pressure symptoms.

Since the diagnosis of Hashimoto’s thyroiditis is not documented by pathologic examination, 9/10 cases (90%) included in the present work were confirmed by correlation with clinical, serological, and follow up radiological studies, the only case (10%) of Hashimoto’s thyroiditis that underwent surgical intervention showed a smear with atypical lymphoid cells, thus biopsy was requested.

In our study, 40 out of 296 (13.5%) cases were diagnosed as FLUS, pathologic diagnosis was follicular adenoma in 31 out of 40 cases (77.5%), and nodular goiter in nine cases (22.5%). Four cases (8.2%) of follicular neoplasm were diagnosed as colloid goiter, 14 cases (28.6%) as follicular carcinoma, 29 cases (59.2%) as follicular adenoma, and two cases (4.1%) as follicular variant of papillary carcinoma. Of the included 30 cases suspicious for papillary carcinoma, 29 cases (96.7%) were confirmed after resection, while the remaining case (3.3%) was proved to be nodular goiter. Forty out of 42 cases (95.2%) of papillary thyroid carcinoma were confirmed histologically, while two cases (4.8%) were diagnosed as papillary hyperplasia. The pathologic diagnosis of all included cases of medullary carcinoma was concordant with the cytologic one (100%) (immunocytochemical reaction of one included case of medullary carcinoma to carcinoembryonic antigen (CEA), chromogranin, and calcitonin was done and showed positive reaction to the three markers Fig. 7).

Of the included 10 cases of anaplastic carcinoma, two (20%) were early resectable, thus underwent surgical resection, one (10%) showed plasmacytoid cells, so biopsy was requested for confirmation and proved to be medullary carcinoma, the

Figure 6 A case of medullary carcinoma showing scattered separate epithelial cells having abundant cytoplasm, and eccentric nuclei (plasmacytoid cells) (Pap. ×400).

Figure 7 A case of medullary carcinoma proved by positive immunocytochemical reaction to carcinoembryonic antigen (CEA), chromogranin, and calcitonin (Pap. ×400).
remaining seven cases (70%) had an advanced stage of cancer and surgical resection was enabled, thus final diagnosis was based on FNAC, in correlation with clinical and radiological (Table 2).

Of the included 98 cases cytologically diagnosed as benign (non-neoplastic), 90 cases (91.8%) were proved to be non-neoplastic (by histopathology and clinico-radiologic follow-up), and eight cases (8.2%) were diagnosed as neoplastic by histopathology. Forty-five out of 49 (91.8%) cases of follicular neoplasm were neoplastic, and four cases (8.2%) were benign by histopathology (non-neoplastic). Among the included 88 malignant and suspicious cases, 85 cases (96.6%) were malignant, while only three cases (3.4%) were proved to be benign by histopathology. Thus, FNAC achieved a sensitivity of 92.8%, specificity of 94.2%, positive predictive value of 94.9%, negative predictive value of 91.8%, and a total accuracy of 93.6% (Table 3).

**Table 2** Cytologic diagnosis of included cases, and the corresponding pathologic results.

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>No.</th>
<th>Pathologic diagnosis</th>
<th>No.</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>50</td>
<td>Benign</td>
<td>42</td>
<td>TN</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>49</td>
<td>Neoplastic</td>
<td>8</td>
<td>FN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colloid goiter</td>
<td>42</td>
<td>TN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follicular neoplasm (adenoma except 1 case papillary carcinoma)</td>
<td>7</td>
<td>FN</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>1</td>
<td>NHL</td>
<td>1</td>
<td>FN</td>
</tr>
<tr>
<td>Follicular lesion of US</td>
<td>40</td>
<td>Follicular adenoma</td>
<td>31</td>
<td>TP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nodular goiter</td>
<td>9</td>
<td>TP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follicular carcinoma</td>
<td>29</td>
<td>TP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nodular goiter</td>
<td>14</td>
<td>TP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papillary carcinoma (follicular variant)</td>
<td>4</td>
<td>TP</td>
</tr>
<tr>
<td>Suspicious</td>
<td>30</td>
<td>Malignant</td>
<td>29</td>
<td>TP</td>
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<tr>
<td>Malignant</td>
<td>51</td>
<td>Malignant</td>
<td>49</td>
<td>TP</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>42</td>
<td>Benign</td>
<td>2</td>
<td>TP</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>6</td>
<td>Medullary carcinoma</td>
<td>6</td>
<td>TP</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>3</td>
<td>Anaplastic carcinoma</td>
<td>2</td>
<td>TP</td>
</tr>
</tbody>
</table>

**Table 3** Relations between cytologic and final diagnosis.

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>Final diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Benign</td>
<td>90 (TN)</td>
<td>8 (FN)</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>4 (FP)</td>
<td>45 (TP)</td>
</tr>
<tr>
<td>Suspicious and malignant</td>
<td>3 (FP)</td>
<td>85 (TP)</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>138</td>
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**Discussion**

Fine needle aspiration cytology is regarded as the gold standard initial investigation in the diagnosis of thyroid swellings. The technique is safe, simple and quick with a low complication rate. Several other tests, such as high resolution ultrasonography, radioisotope scanning and others have been used for evaluation of thyroid swellings before proceeding to thyroid surgery. Studies have demonstrated that among all these diagnostic modalities, FNAC is the most accurate, cost effective screening test for rapid diagnosis of thyroid swellings [9].

Fine-needle aspiration cytology has greatly improved the clinical management of thyroid nodules. However, FNA has inherent limitations related not only to inadequate sampling but also, most importantly, to its inability to distinguish between benign and malignant follicular lesions in the absence of nuclear features of papillary carcinoma. The indeterminate diagnosis of follicular neoplasm encompasses a number of heterogeneous thyroid lesions including cellular adenomatoid nodule, follicular adenoma, and follicular carcinoma [10]. Additionally, the interpretation of follicular variant of papillary carcinoma (FVPC) in cytology may be difficult when prominent classic nuclear features of papillary thyroid carcinoma are absent. In such cases, a preoperative diagnosis of “follicular lesion suggestive of papillary carcinoma” results in conservative surgical assessment until a definitive diagnosis can determine the appropriate treatment [11]. Another limitation of FNAC is the presence of false negative and positive results particularly with small tumors and when there is associated degenerative or inflammatory change in adjacent thyroid tissue. In addition, there is a group of lesions which overlap benign and malignant features. For instance, the distinction between a cellular colloid goiter and a follicular neoplasm may be impossible [12].

As reported in other literatures, age and gender were associated factors of thyroid lesions [13]. In present study, there was a female predominance giving a female-to-male ratio of 5.2:1. The age of patients ranged from 14 to 77 years, with median of 44 years, being slightly higher in neoplastic lesions (45 years) than in non-neoplastic lesions (40 years).

As in other literature, the benign cases represented the majority of cases (33.1%). The incidence of specific histology in the benign and malignant group showed no difference from other reports [13]. Nodular hyperplasia constituted the majority of benign lesions (89.8%). Papillary carcinoma was the most frequent malignant lesion, with an incidence of...
(72.4%), while anaplastic (17.2%) and medullary carcinomas (10.3%) were the second and third most common malignant lesions, respectively.

Every thyroid FNA must be evaluated for adequacy. Inadequate samples were reported as “nondiagnostic” or “unsatisfactory.” This category applies to specimens that were unsatisfactory owing to obscuring blood, overly thick smears, air drying of alcohol-fixed smears, or an inadequate number of follicular cells. For a thyroid FNA specimen to be satisfactory for evaluation, at least six groups of benign follicular cells are required, each group composed of at least 10 cells. Published data suggest inadequate sample range between 2% and 20% [14]. In our study the inadequate sample rate was 7.1%.

In our series, analysis of data revealed a sensitivity of 92.8% and a specificity of 94.2%, which was translated into a diagnostic accuracy of 93.6%, a PPV of 94.9%, and a NPV of 91.8%. Our results were comparable with published data where FNAC of thyroid is reported to have a sensitivity ranges from 65% to 98%, a specificity of 72% to 100%, a positive predictive value of 34% to 100%, and a negative predictive value of 83% to 100% [15]. Determinant factor for such a wide range of difference may be due to differences in number of cases, the included diagnostic categories, and how the cytopathologists classify ‘suspicious’, FLUS, as well as false positive and negative samples. Some authors include follicular lesion in the neoplastic group, whereas others exclude them from the calculations [16].

The incidence of FLUS cases in our study was 13.5%, which is higher than the reported figure of 3-6% in literature [17]. This could be explained by the subjective nature of the cytomorphologic diagnostic features of this category between different cytopathologists interpreting the cases in our unit where we are recently introducing the Bethesda system.

The overall accuracy of cytologic diagnosis in our study was 93.6% which agrees more or less with published data that approach 95% in the differentiation of benign from malignant nodules of the thyroid gland [4]. However, the interpretation errors in this study can be reduced by obtaining aspirates from different portions of the lesion, using ultrasound-guided FNA procedure, and reviewing slides by more than one cytopathologist [18].

The false negative rate (FNR) is defined as the percentage of patients with benign cytology in whom malignant lesions are later confirmed on thyroidectomy. The false negative FNAC results may occur because of sampling error, coexistence of benign and malignant lesions, or cytomorphologic overlap between benign and low grade malignant tumors. This is of great concern because it indicates the potential to miss malignant lesion [19]. However, it is difficult to calculate the true false negative rate because only a small percentage (approximately 10%) of patients with benign cytological findings proceed to surgery. FNR ranged from 1% to 16% in different series [20].

In our series FNR was 5.8%, which agrees with that reported in literature. There were six out of 49 cases (12.2%) of nodular goiter proved to be follicular adenoma, and one case (2%) as follicular carcinoma. There was also one out of 10 cases (10%) of Hashimoto’s thyroiditis proved histopathologically to be NHL.

On review, smears from the seven cases of colloid goiter with false negative cytologic diagnosis showed moderate cellularity with small clumps of thyroid follicular cells arranged in poorly cohesive groups with some colloid in background suggesting the diagnosis of nodular colloid goiter. Aspiration in these cases was probably done from a hyperplastic adenomatous nodule. In general, cytological differentiation between follicular neoplasm and adenomatous goiter is not confusing, although sometimes seems very difficult [21]. As a general rule, smears from adenomatous goiter show less cells and more colloid than those from follicular neoplasm. In some rare occasions, confusing cellular smears are detected in non-neoplastic adenomatous nodules. In such rare cases, the presence of dispersed rather than tightly cohesive follicular cells is in favor of non-neoplastic adenomatous nodule. Also, thyroid scintigram may solve this problem, where neoplastic nodules appear as cold nodules [22].

An associated neoplastic lesion, not rarely encountered in cases of Hashimoto’s thyroiditis, and that is not properly sampled by FNA, could explain missing of a lymphomatous focus in some cases of Hashimoto’s thyroiditis and resulted in increasing the incidence of false negative diagnosis of NHL. Thus, if lymphoma is suspected, demonstration of monoclonality by immunostaining, and flow cytometric studies performed on the aspirate may help in determining a definitive diagnosis without having to restore to surgery [23].

The false positive rate (FPR) indicates that a patient with malignant FNAC result was found on histological examination to have benign lesion. In our series the FPR was 7.2% which agrees with other series that ranged from 0% to 8% [18]. We reported three cases (3.1%) as malignant and suspicious for carcinoma, and four cases (4.1%) of follicular neoplasm that proved to be non-neoplastic on histologic correlation.

The four cases of follicular neoplasm showed clusters of follicular cells arranged in clumps with scanty colloid. The histology though, showed features of a nodular colloid goiter. Aspiration was probably done from the hypercellular areas of colloid nodules which led to over diagnosis. As already discussed, cytological distinction between these two conditions is often difficult. A possible remedy is multiple aspirations from different parts of the swelling that could demonstrate hypocellular, polymorphic, and colloid-rich areas. Demonstration of monolayered sheets of epithelial cells representing macrofollicles and degenerative changes would suggest the possibility of non-neoplastic lesions [24].

The cytological smears of two cases wrongly diagnosed as papillary carcinoma were moderately cellular showing numerous macrophages, thick colloid, cohesive clumps and sheets of follicular cells arranged in vague papillary patterns with nuclear overlapping and crowding. Few cells contained moderate amount of blue cytoplasm and round nucleus with pale open chromatin. Intranuclear inclusions were demonstrated in few cells. The histology showed features consistent with those of a nodular colloid goiter. Misinterpretation of partly degenerated non-neoplastic follicular cells, focal papillary architecture, and intranuclear inclusions were probably the causes of error in these cases. Multiple samples collected from different parts of the lesion could help in proper diagnosis. For cytdiagnosis of papillary thyroid cancer, the most important features suggested are intranuclear cytoplasmic inclusions, dense metaphasic cytoplasm, and papillary structures with distinct anatomical border. These features can lead to a decrease in the wrong cytologic diagnosis of papillary thyroid carcinoma [25].

On review, smears from the seven cases of colloid goiter with false negative cytologic diagnosis showed moderate cellularity with small clumps of thyroid follicular cells arranged in poorly cohesive groups with some colloid in background suggesting the diagnosis of nodular colloid goiter. Aspiration in these cases was probably done from a hyperplastic adenomatous nodule. In general, cytological differentiation between follicular neoplasm and adenomatous goiter is not confusing, although sometimes seems very difficult [21]. As a general rule, smears from adenomatous goiter show less cells and more colloid than those from follicular neoplasm. In some rare occasions, confusing cellular smears are detected in non-neoplastic adenomatous nodules. In such rare cases, the presence of dispersed rather than tightly cohesive follicular cells is in favor of non-neoplastic adenomatous nodule. Also, thyroid scintigram may solve this problem, where neoplastic nodules appear as cold nodules [22].

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Many thyroid cancers, especially papillary thyroid carcinoma, can be diagnosed with certainty by FNA. However, the nuclear and architectural changes of some PTCs are subtle and focal. This is particularly true for the follicular variant of PTC, which can be difficult to distinguish from a benign follicular nodule. Other PTCs may be incompletely sampled and yield only a small number of abnormal cells [26]. If only 1 or 2 characteristic features of PTC are present, or if they are only focal and not widespread throughout the follicular cell population, a malignant diagnosis cannot be made with certainty. Such cases are best classified as “suspicious for malignancy”. Nodules called suspicious for papillary carcinoma are resected by lobectomy or thyroidectomy. Most prove to be papillary carcinomas, and the rest are usually follicular adenomas [27,28]. The same general principle applies to other thyroid malignancies like medullary carcinoma and lymphoma, but these are encountered less frequently than PTC. Ancillary techniques (immunohistochemistry, flow cytometry) in borderline cases is usually more helpful with medullary carcinoma and lymphoma than with PTC [29]. In our study, there were 30 cases reported as suspicious for papillary carcinoma, as the nuclear morphologic features were only focal in some cases, while in others, not all the features were seen. Twenty-nine out of 30 cases (96.7%) were proved after pathologic examination, while only one case (3.3%) was nodular goiter.

Two cases of a follicular variant of papillary carcinoma (FVPTC) were wrongly interpreted as follicular neoplasm. The smears had shown numerous follicular cells arranged in clusters, often with syncytial cell aggregates. There was prominent nuclear crowding and overlapping without any colloid. The presence of follicular structures led to misinterpretation. A possible way to reduce such error is to do aspirations from different parts which could reveal the typical nuclear features of papillary carcinoma [30]. A group of authors reported that papillary nuclear features in more than 20 cells would have a greater risk of occurrence of papillary carcinoma, although these findings may also lead to over interpretation [31].

The smears from one case of anaplastic carcinoma showed numerous cells with plasmacytoid features, thus biopsy was requested and proved to be medullary carcinoma. Generally, medullary carcinoma of giant cell type may appear cytologically identical to anaplastic carcinoma. Application of immunostaining for calcitonin, or electronmicroscopy can solve the problem [32].

In conclusion, the results of our study are comparable with the current published data and demonstrate that FNA cytology is a sensitive, specific, and accurate initial diagnostic test for evaluation of patients with thyroid swellings. Cytodiagnostic errors of some cases with overlapping cytological features can be avoided by paying attention to the possible pitfalls. The suspicious results can be resolved by diagnostic surgical resection. A benign FNAC diagnosis should be viewed with caution as false negative results do occur and these patients should be followed up clinico-radiologically for any progression that will require repeated FNAC and/or surgery.

References