The diagnostic value of fine-needle aspiration cytology in the assessment of thyroid nodules: a retrospective 5-year analysis

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Objective. To audit the diagnostic accuracy and value of fine-needle aspiration cytology in the assessment of thyroid nodules over a 5-year period.
Design. Retrospective study.
Setting. Private practice, Hong Kong.
Patients. The computerised records from cytological and histological examinations of all thyroid specimens submitted from 1993 through 1997 were studied; the 1236 aspirates came from 1033 women and 175 men (gender was not specified in 28 cases).
Main outcome measures. Cytological reports were classified diagnostically, and histological and cytological correlations were determined.
Results. Of the 1236 aspirates, 113 (9.1%) were unsatisfactory; 1013 (82.0%), including cysts, were benign; and 110 (9.0%) were neoplastic or malignant. Histological follow-up was available for 149 cases; 13 were unsatisfactory for cytological diagnosis. Statistical analysis of the remaining 136 cases yielded the following results: sensitivity of fine-needle aspiration cytology, 56%; specificity, 90%; positive predictive value, 74%; negative predictive value, 80%; accuracy, 79%. These results were within the range of previously published values. The sensitivity was improved by combining clinical information: if nodules larger than 3-cm diameter were excised (despite a non-neoplastic aspiration cytology report), the sensitivity increased to 71% and the accuracy to 84%.
Conclusion. Fine-needle aspiration cytology is an effective screening test to help evaluate whether surgery is required in the management of thyroid nodules. False-positive and false-negative rates can be minimised by taking clinical and imaging data into consideration.

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Key words: Biopsy, needle; Cytodiagnosis; Predictive value of tests; Sensitivity and specificity; Thyroid neoplasms

Introduction

Thyroid nodules are common, occurring in 4% to 7% of the population,[1] and affect women more commonly than they do men. Excising all thyroid nodules is impractical, as most thyroid nodules are benign and thyroid surgery is not without risks. An effective screening test is therefore needed to identify patients who require surgery. Before the widespread acceptance of fine-needle aspiration (FNA) cytology, ultrasonography and nuclear medicine imaging were the main investigations of thyroid nodules. Ultrasonography can distinguish between solid and cystic lesions, but many 'solid' nodules are benign colloid nodules and not all cystic lesions are benign. Isotope scans can be used to classify nodules as 'hot' (functioning) or 'cold' (non-functioning). While functioning nodules are usually benign, however, fewer than 20% of non-functioning nodules are malignant. Thus, imaging techniques have a rather low sensitivity and specificity. Furthermore, imaging is relatively expensive and hence unsuitable as a screening test.

Fine-needle aspiration cytology has been advocated as the first investigation of choice when assessing thyroid nodules.[2] The procedure is relatively simple and cheap, and can be performed in a doctor's office with relatively few complications. The effectiveness

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of FNA cytology in the assessment of thyroid nodules is well documented and the technique can reduce the percentage of people requiring surgery for a non-neoplastic lesion—from 40% to 3% of the screened population.[3,4] A study of specimens submitted during a 5-year period to the Histopathology Unit at the Canossa Hospital for FNA cytology was conducted to evaluate the effectiveness of the test in Hong Kong.

Materials and methods

The computerised records from the FNA and histological examinations of all thyroid specimens submitted to the Histopathology Unit at the Canossa Hospital from January 1993 to December 1997 were retrieved. The reports, including patient demographic data, were analysed. All FNAs had been performed by clinicians and radiologists, and smears or fluid had been submitted to our laboratories for reporting. Some smears had been wet-fixed and stained with Papanicolaou stain, whereas some had been air-dried and stained with the 'Diff-Quik' stain (Dade diagnostic, Aguada, Puerto Rico). The number of FNA smears obtained from each patient varied from one to 18 slides. Cytospin slides were made from the fluid using a Shandon cytocentrifuge (Life Sciences International Ltd., Cheshire, United Kingdom). The methods and sizes of needles used by the aspirators were not recorded. The smears were randomly assigned before the study.

Diagnostic criteria

The FNA reports were grouped into the following categories: non-diagnostic (unsatisfactory), thyroiditis (including de Quervain's thyroiditis), cyst, benign follicular pattern (BFP), atypical follicular pattern (AFP), suspicious for papillary carcinoma, papillary carcinoma, and 'other carcinoma and lymphoma'. Smears were considered to be non-diagnostic if there were fewer than six clusters of follicular cells, regardless of whether there was colloid or other cellular material present in the smears. Cases were diagnosed as thyroiditis if there were abundant lymphocytes in the background; there was often associated oncocytic or Hürthle cell change in the follicular epithelium. Multinucleated giant cells were present in cases classified as de Quervain's thyroiditis.

Contents of cysts were most often submitted as fluid, and their cytospin smears showed cellular debris, colloid-like material, and macrophages; epithelial cells were rarely present. We routinely add a caveat in our reporting of a cyst to the effect that we cannot define the underlying lesion (as no epithelial cells are visible) and hence follow-up is advisable. Smears described as having a BFP contained a scant to moderate amount of follicular cells that were often arranged in flat sheets or in a macrofollicular pattern. Occasionally, the BFP smears contained a large proportion of cells. Round or oval nuclei that were dissociated and bare—presumably follicular cells stripped of cytoplasm—were present in varying quantities in the background. A moderate amount of colloid was usually present in the background. The BFP category was intended to include normal thyroid, colloid nodules, and hyperplastic nodules. Cases that were classified as having an AFP usually contained cellular material in moderate to high abundance. The follicular epithelia were arranged in three-dimensional clusters that imparted a 'syncytial' pattern and in small dissociated groups that resembled microfollicles. A repeating microfollicular pattern was observed in some cases. Colloid was sometimes present but never in a significant amount. Papillary carcinoma cases were usually very cellular and contained numerous cell clusters and occasionally papillary fragments. The nuclei of the tumour cells were elongated or oval, had a fine chromatin pattern, showed grooving, and contained intranuclear inclusions. Cases that fulfilled some but not all cytological criteria were reported as being suspicious for papillary carcinoma and included cases of a follicular variant of papillary carcinoma. The 'other carcinoma and lymphoma' cases contained cells that had definite malignant nuclear morphology.

Data analysis

Non-diagnostic cases were excluded from the statistical analyses. For the purpose of statistical analysis, cases of cyst, thyroiditis, and BFP were classed as being benign and the remaining cases were classed as being neoplastic. True negative (TN) cases were reported as being a cyst or thyroiditis, or having a BFP by FNA cytology; they were also shown to be benign following histological examination (with the exception of follicular adenoma). False negative (FN) cases were reported as being benign by FNA cytology but were shown to be neoplastic (including follicular adenoma) following histological examination. True positive (TP) cases were reported as having an AFP or being malignant by FNA cytology and were neoplastic (including follicular adenoma) following histological examination. False positive (FP) cases were reported as having an AFP or being a carcinoma by FNA cytology but were benign non-neoplastic lesions following histological examination. The diagnostic accuracy was calculated using the formula [(TP+TN)x100]/(TP+TN+FP+FN).

The slides from the cytological and histological examinations of all false positive and false negative cases were retrieved and reviewed. The smears were reviewed without knowledge of the previous diagnoses. Tumour sizes were recorded in discrepant cases.

Results

There were 1236 FNA samples of the thyroid from 1033 women and 175 men; patient gender was not stated in 28 cases. The mean age was 42 years (range, 13-84 years) for women and 47 years (range, 14-83 years) for men. The diagnostic categories of the FNA cases are shown in Table 1. The non-diagnostic (unsatisfactory) category accounted for 113 (9.1%) of all cases and were not included in further statistical analysis. Benign categories accounted for 1013 (82.0%) of the 1236 FNA cases, and neoplastic and suspicious cases together constituted 110 (9.0%) of cases. During the same study period, 1060 surgical thyroid specimens were obtained. Follow-up histological information was available for 149 (12%) of all FNA cases. The cytology-histology correlation of these 149 cases is shown in Table 2. Biopsies were more commonly performed in women (129; 12.5%) than in men (19; 10.8%); patient gender was not known in one case.

Table 1. Diagnostic categories of fine-needle aspirations of the thyroid

Diagnostic category	No. of samples (%)
Non-diagnostic	113 (9.1)
Cyst	414 (33.5)
Thyroiditis	59 (4.8)
Benign follicular pattern	540 (43.7)
Atypical follicular pattern	86 (7.0)
Suspicious for papillary carcinoma	7 (0.6)
Papillary carcinoma	13 (1.0)
Carcinoma (anaplastic, medullary, not otherwise specified)	3 (0.2)
Lymphoma	1 (0.1)
Total	1236

Of the 1013 patients whose samples were classified as being benign (non-neoplastic), 102 (10.1%) had undergone surgery; neoplasms were found in 20 (ie false negative) cases: 19 cases of follicular adenomata and one papillary carcinoma. The latter case was clinically suspicious and the nodule measured 3 cm in diameter. Following cytological review, however, this case was reclassified as having an AFP, owing to the presence of repeating microfollicles and absence of cytological features of papillary carcinoma. Eleven cases of follicular adenomata had been diagnosed as having a BFP; three of these actually had an AFP following cytological review due to the presence of microfollicles. Of the 11 follicular adenomata biopsy samples, four (including one that had a revised diagnosis of AFP) were nodules larger than 3 cm in diameter. Review of the cases that had been diagnosed as a cyst identified one case of AFP in which scant thyroid follicular epithelium was arranged in a microfollicular pattern and in which the background contained abundant colloid and 'foamy' macrophages. This lesion was 4 cm in diameter. Two other cystic lesions measured more than 3 cm in diameter.

Of the 110 FNA cases that had been diagnosed as being neoplastic (ie AFP and malignant cases), follow-up biopsy specimens were available in 34 (30.9%) cases. There were nine false positive cases; one showed dyshormonogenetic goitre and 8 showed nodular hyperplasia. On cytological review, the case of dyshormonogenetic goitre showed highly cellular smears, clusters and sheets of follicular cells that were arranged in a microfollicular pattern, and a background of scant colloid. Two of the seven nodular hyperplasia samples that had been classed as having an AFP were moderately cellular, but the follicular cells were arranged mostly in flat sheets and there was no microfollicular pattern. They were thus subsequently revised to cases of BFP.

Table 2. Cytohistological correlation of fine-needle aspirations of the thyroid

	Histology								
FNA*	DG†	Cyst	Thyroiditis	DH‡	NH§	FA[xx]	PC¶	Carcinoma	Total
Non-diagnostic	-	-	-	-	7	4	2	-	13
Cyst	-	9	-	-	16	8	-	-	33
Thyroiditis	-	-	-	-	1	-	-	-	1
BFP**	-	1	1	1	53	11	1	-	68
AFP††	1	-	-	-	6	10	8	2	27
PC	-	-	-	-	2	-	5	-	7
Total	1	10	1	1	85	33	16	2	149

* FNA fine-needle aspiration
† DG dyshormonogenetic goitre
‡ DH diffuse hyperplasia
§ NH nodular hyperplasia
[xx] FA follicular adenoma
¶ PC papillary carcinoma
** BFP benign follicular pattern
†† AFP atypical follicular pattern

Table 3. Summary of statistical analyses*

Cytology	Histology	
	Non-neoplastic	Neoplastic
Non-neoplastic	82 (TN†)	20 (FN‡)
Neoplastic	9 (FP§)	25 (TPxx)
Sensitivity = (TPx100)/(TP+FN) = 56%		
Specificity = (TNx100)/(TN+FP) = 90%		
Positive predictive value = (TPx100)/(TP+FP) = 74%		
Negative predictive value = (TNx100)/(TN+FN) = 80%		
Accuracy = [(TP+TN)x100]/(TP+TN+FP+FN) = 79%		

* Excluding 13 cases with non-diagnostic cytology (n=136)
† TN true negative
‡ FN false negative
§ FP false positive
xx TP true positive

Both cases of false negative diagnoses of carcinoma were highly cellular and contained many papillary-like fragments. However, these fragments lacked fibrovascular cores, and nuclear changes typical of papillary carcinoma were also absent. On cytological review, the diagnoses of these two cases were changed to BFP. Histological examination of these two cases showed nodular hyperplasia and focal degenerative areas of pseudopapillary hyperplasia.

Analysis of the results showed FNA cytology to have a sensitivity of 56%, specificity of 90%, positive predictive value of 74%, negative predictive value of 80%, and an accuracy of 79% (Table 3).

Discussion

Fine-needle aspiration cytology of the thyroid is considered to be the most effective screening test for investigating thyroid nodules. The sensitivity and specificity of FNA cytology of the thyroid are lower compared with the cytology of other body sites due to the intrinsic difficulties in diagnosing endocrine neoplasia. For example, the cells of a follicular adenoma are morphologically and cytologically similar to those of a follicular carcinoma. A carcinoma is diagnosed by the presence of capsular or vascular invasion, which can only be assessed histologically. Because of the difficulty in distinguishing between an adenoma and a carcinoma, a common FNA diagnosis of follicular neoplasm is given. We prefer to use the alternative term of AFP as the FNA diagnosis, because aspirates of a cellular hyperplastic nodule cannot always be distinguished from those of a follicular neoplasm. Other groups[3,5] have encountered the same problem and have used other terms such as cellular adenomatoid lesion. Thus, we consider FNA cytology of the thyroid to be a screening test rather than a diagnostic test (which FNA cytology is viewed to be for other anatomical sites such as the breast).

The results of previous studies show a fairly wide range of sensitivities (53%-95%), specificities (52%-100%), positive predictive values (46%-100%), negative predictive values (69%-97%), and accuracies (65%-83%), partly owing to the different methodologies and classification systems used (Table 4).[3,5-10] The corresponding values from this study fall within the ranges reported. However, the sensitivity of FNA cytology was at the lower end of the range, perhaps due to the very disparate quality and quantity of cells in the smears submitted by clinicians who had varying experiences in performing an FNA biopsy.

As with other screening tests, the sensitivity and specificity can be improved when clinical criteria

Table 4. Results from previous studies of fine-needle aspiration of the thyroid

Study	No. of FNAs*	No. of histological samples	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Insufficient for diagnosis	Accuracy
Kendall,[3] 1989	113	34	-	-	-	-	6	-
Piromalli et al,[6] 1992	795	216	95	98	95	97	-	-
Godinho-Matos et al,[7] 1992	144	28	73	100	100	69	13	83
Mandreker et al,[8] 1995†	1992	238	53	93	82	78	12	79
Holleman et al,[9] 1995	112	53	84	52	53	83	11	65
Burch et al,[10] 1996	504	-	80	73	-	-	-	75
Leonard and Melcher,[5] 1997	335	184	88	78	46	97	18	80
Present report	1236	149	56	90	74	80	8	79

* FNAs fine-needle aspirations
† Results were calculated in the same way and based on the same criteria as this report

such as nodules of larger diameter, fixation to another structure, and younger patient age are taken into consideration.[11] If all thyroid nodules larger than 3 cm were considered neoplastic and then excised, regardless of the FNA cytology diagnosis, the sensitivity in our series would have increased to 71% (since seven of the false negative cases were nodules greater than 3 cm), compared with 56% (Table 3). It is thus important to stress that a negative FNA report does not exclude a neoplasm, especially if there are other clinical or imaging data that suggest the contrary. Further improvement can be made by applying more rigid cytological criteria. Two AFP and two carcinoma cases were rediagnosed as having a BFP, and four BFP cases and one cyst were rediagnosed as having an AFP when more stringent criteria were followed. When the revised FNA diagnoses and the 3-cm criterion were accounted for in the statistical analyses, a sensitivity of 75%, specificity of 96%, positive predictive value of 87%, negative predictive value of 88%, and an accuracy of 88% were obtained. Another documented pitfall or source of error is the existence of cystic lesions, which are usually poorly cellular.[12] If surgical resections were performed on recurrent cysts, as advocated by Woeber,[4] diagnostic parameters may be further improved.

Most published series on FNA cytology of the thyroid have come from large institutions, where the samples have been obtained by pathologists or a few dedicated clinical aspirators. This study used samples from many different clinicians of varying experience and showed that comparable results can be obtained.

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