VALIDITY OF FINE NEEDLE ASPIRATION CYTOLOGY IN THE DIAGNOSIS OF THYROID DISEASES

D H Beneragama,[1] W Jayasuriya,[2] R I U Samarawickrama,[3] R A T K Rupasingha,[3] M G Y Piyasena,[3] U H J P Dayarathna,[3] S D S P Dissanayake[3]

Departments of [1]Pathology, [2] Community Medicine and [3]12th batch of medical students (2002/03), Faculty of Medical Sciences, University of Sri Jayewardenepura

Abstract

Introduction: Fine needle aspiration cytology (FNAC) is regarded as an important first line investigation for evaluation of thyroid swellings. It has a diagnostic accuracy of over 90% in terms of specificity, sensitivity and predictive values.

Objective: The aim of this study was to determine the validity (specificity, sensitivity positive/negative predictive values) of FNAC in the diagnosis of thyroid diseases.

Methods: FNAC reports and histopathology reports of patients with thyroid diseases, who have undergone surgery, were retrospectively retrieved from data banks in the Department of Pathology, University of Sri Jayewardenepura, from August 2004 to August 2006. In addition a prospective study in patients with thyroid diseases who came to this unit for FNAC from June to September 2006 was carried out. In all the cases the histological diagnosis was compared with the cytological diagnosis and the results were documented and analyzed by using standard statistical methods.

Results: FNAC has an acceptable validity in the diagnosis of thyroid diseases with high specificity (86.74%), sensitivity (84.05%), positive predictive value (84.05%) and negative predictive value (86.74%).

Keywords: thyroid cytology, specificity, sensitivity, positive and negative predictive values.

Address for correspondence: D.H. Beneragama, Department of Pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.
e-mail: dulani.ben@gmail.com

Introduction

Thyroid diseases are a common clinical problem worldwide. The incidence of thyroid cancers is approximately 122,000 new cases per year worldwide.[1] In Sri Lanka, thyroid cancers are responsible for 4.6% of all cancers and account for 6.9% of cancers in females.[2]

Fine Needle Aspiration Cytology (FNAC) is widely accepted a simple and minimally invasive investigation in the assessment of nodular thyroid disease and has shown to have a high sensitivity in diagnosing malignancies as well as in the evaluation of thyroid nodules.[3]

At present, in Sri Lanka, FNAC is used as a routine first line diagnostic method to assess thyroid diseases. As it is a simple technique which can be carried out in the out-patient department, it can be readily repeated if necessary, and has good patient compliance. FNAC is therefore used as the key investigation in combination with radiological investigations in many recognized centers to assess discrete thyroid swellings to diagnose or exclude a malignancy. FNAC has also reduced the need of isotope scans & the necessity for surgery.

Thyroid nodules that are considered for FNAC include firm, palpable, solitary nodules, nodules associated with suspicious clinical or ultrasonographic features, dominant nodules in a multinodular goiter, recurrent cystic nodules, and a nodules associated with palpable lymph nodes.[4]

Several studies based on different methodologies have reported a high degree of sensitivity, specificity, positive and negative predictive values of FNAC for thyroid.[5] It has a diagnostic accuracy of over 90% in terms of predictive value, sensitivity and specificity in the diagnosis of malignancy. Accuracy of the diagnosis has been shown to increase with the experience of the pathologist.[5,6]

The procedure involves aspiration of the thyroid by a 10ml syringe attached to a fine needle (23-25 gauged). Tissue sludge, tissue fragments and blood are aspirated and smeared on glass slides. One slide is usually air dried and stained with May-Grunwald-Giemsa stain and the other smear is fixed in alcohol and stained by Haematoxylin and Eosin stain or Papanicolaou stain. Ideally the aspiration should be performed by a pathologist who then reads the smears.[7-9]

Although FNAC is considered as a highly sensitive investigation, it is always reproducible. The false positive rate is low with respect to malignancy, but there is definitely a higher false negative rate especially in follicular neoplasm.[9,10]

There can be high rate of unsatisfactory aspirates particularly in cystic swellings due to a low cellular yield. It can result in non representative samples especially in dominant nodules of a multinodular goiter unless the surgeon marks the dominant nodule. The use of ultrasound guided aspirations has helped to overcome this problem in obtaining representative samples.

Although FNAC entails some difficulties in small thyroid enlargements, and sampling errors in inexperienced hands it can be a rapid and useful diagnostic investigation.

The current study was carried out to assess the sensitivity, specificity, & negative and positive predictive values of FNAC.

Sensitivity: the proportion of the true positives among those having the disease.

Specificity: the proportion of true negatives among those not having the disease.

Positive predictive value: the probability of the person having the disease when the test is positive.

Negative predictive value: the probability of the person not having the disease when the test is negative.

Material and methods

The study was a descriptive study carried out on patients who were admitted to Colombo South Teaching Hospital (CSTH). FNAC reports and histopathology reports of patients with thyroid diseases, who have undergone surgery, were retrospectively retrieved from data banks in the department of pathology, USJP, for a period of three years from August 2004 to September 2006. In all the cases, the histological and cytological diagnoses were documented, compared and analyzed using standard statistical formulae (Non-probability sampling). Sample size was calculated using standard formula with the minimum sample size estimated as 50.

(1) Data collection

1. Identification of variables

Number of Benign thyroid diseases (E.g. Colloid goiters /Thyroiditis)

Number of malignant thyroid diseases (E.g.: Papillary carcinoma/ Follicular carcinoma/Other).

2. Study instruments

Data extraction sheets. (FNAC reports & histological reports).

3. Data collection proper

Data from the FNAC report of each patient and the corresponding histology report was collected and tabulated for analysis.

(2) Data Analysis

Data analysis was carried out manually according to the standard analytical methods.

$$\text{Sensitivity} = \frac{a}{a+c} \qquad \text{Positive predictive value} = \frac{a}{a+b}$$

$$\text{Specificity} = \frac{d}{b+d} \qquad \text{Negative predictive value} = \frac{d}{c+d}$$

Results

Data from 158 patients who underwent FNAC and who had subsequent histology results were collected and of the above 6 were excluded due to inadequate information given for a conclusive diagnosis. Histological and cytological analysis showed 83 (54.60%) non-neoplastic conditions and 69 (45.39%) neoplastic conditions.

Table 1. The numbers of each neoplastic and non-neoplastic disease on FNAC and histology.

	FNAC - number of cases	Histology - number of cases
Multinodular Goiter	13	09
Thyroiditis	08	13
Colloid Nodule	62	61
Papillary Carcinoma	22	24
Follicular Neoplasm	46	44
Hurthle Cell carcinoma	01	01
Total	152	152

Table 2. Comparison of FNAC diagnosis with the corresponding histological diagnosis.

		Histological diagnosis		
		Neoplastic	Non- neoplastic	Total
FNAC Results	Neoplastic	58 (=a, true positives)	11 (=b, false positives)	69 (a+b)
	Non-neoplastic	11 (=c, false negatives)	72 (=d, true negatives)	83 (c+d)
	Total	69 (a+c)	83 (b+d)	152

Number of true positives	= a	= 58	Sensitivity	= 84.05%
Number of false positives	= b	= 11	Specificity	= 86.74%
Number of false negatives	= c	= 11	Positive predictive value	= 84.05%
Number of true negatives	= d	= 72	Negative predictive value	= 86.76%

Table 3. Validity of FNAC in the diagnosis of each thyroid disease.

Thyroid diseases	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Colloid goiter	82.25%	87.77%	82.25%	87.25%
Autoimmune thyroiditis	66.66%	99.28%	88.89%	97.20%
Multinodular goiter	87.50%	95.13%	50.00%	99.27%
Follicular neoplasm	68.18%	85.18%	65.21%	86.79%
Papillary carcinoma	75.00%	96.87%	81.81%	95.38%

Table 4. Results of false positives and false negatives.

	FNAC Diagnosis	Histological Diagnosis	Number of cases
False positives (Total=11)	Follicular neoplasm	Thyroiditis	4
	Follicular neoplasm	Colloid goiter	6
	Papillary carcinoma	Thyroiditis	1
False negatives (Total=11)	Colloid nodule	Follicular carcinoma	3
	Colloid nodule	Follicular adenoma	8

Example of a true negative- Diagnosis of a colloid nodule (Figures 1a & 1b):

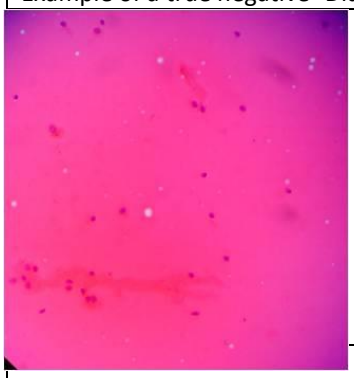

Figure 1a. Cytology of the colloid nodule - Scattered thyroid epithelial cells in a background of abundant colloid (Haematoxylin and Eosin x400)

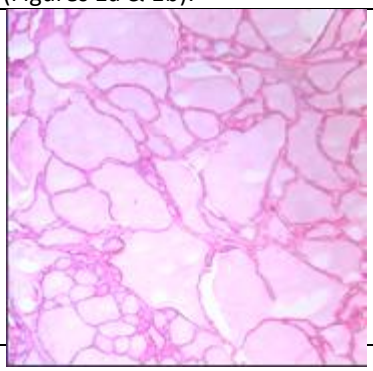

Figure 1b. Histology of the colloid nodule – Colloid filled follicles lined by flattened thyroid epithelial cells (Haematoxylin and Eosin x400)

Example of a true positive- Diagnosis of papillary carcinoma (Figures 2a & 2b):

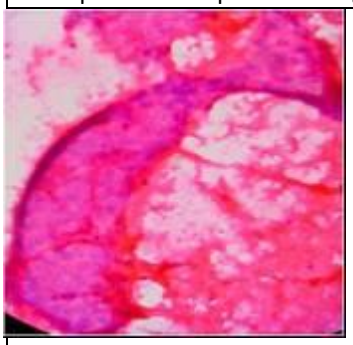

Figure 2a. Cytology of Papillary carcinoma – Thyroid epithelial cells with intranuclear grooves and inclusions, in a papillary configuration (Haematoxylin and Eosin x400)

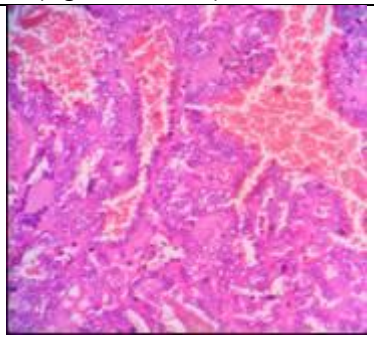

Figure 2b. Histology of Papillary carcinoma – Papillary structures lined by thyroid epithelial cells with intranuclear grooves and pseudoinclusions (Haematoxylin and Eosin x400)

False positive diagnosis of a case of thyroiditis as a follicular neoplasm (Figures 3a & 3b):

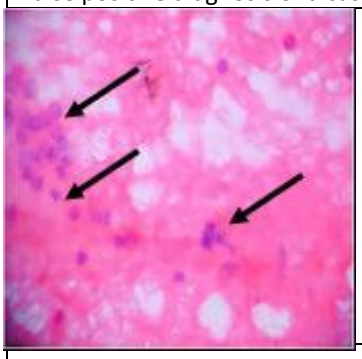

Figure 3a. Follicular neoplasm (FNAC) - Proliferation of microfollicles (arrows) (Haematoxylin &Eosin x400)

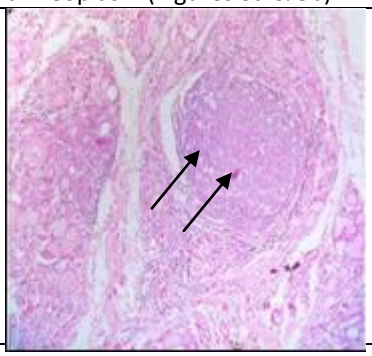

Figure 3b. Thyroiditis (Histology) - lymphoid follicular hyperplasia (double arrow) (Haematoxylin &Eosin x100)

False negative diagnosis of a case of a follicular carcinoma as a colloid nodule (Figures 4a & 4b):

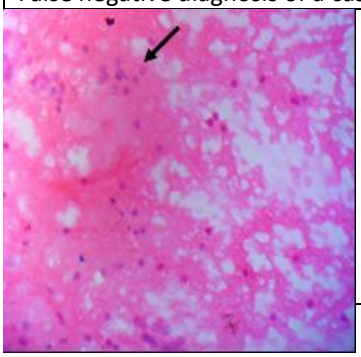

Figure 4a. Colloid nodule (cytology) - Scattered thyroid epithelial cells in a vague follicular configuration (arrow) (Haematoxylin & Eosin x100)

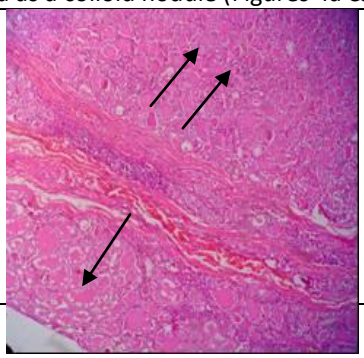

Figure 4b. Follicular carcinoma (histology) - Follicular carcinoma (double arrow) with surrounding thyroid showing features of colloid storage (single arrow) (Haematoxylin & Eosin x400)

At present in Sri Lanka, FNAC is used as a routine diagnostic method for thyroid disease. The current study is the first in Sri Lanka to ascertain the specificity, sensitivity and the positive and negative predictive values of FNAC.

The FNAC diagnoses included 13/152 multinodular goiters, 8/152 thyroiditis, 62/152 colloid nodules, 22/152 papillary carcinomas, 46/152 follicular neoplasm, 1/152 Hurthle cell neoplasm.

The most common non-neoplastic thyroid condition was colloid goiter, which accounted for 78% of all non-neoplastic conditions and is similar to the published data.[8] Out of the neoplastic conditions, follicular neoplasms are the commonest and it includes both follicular adenoma and follicular carcinoma. Other researchers have found papillary carcinoma as the commonest.

In the current study, the sensitivity, specificity, positive predictive value and negative predictive value were 84.05%, 86.74%, 84.05%, and 86.76% respectively. These values are comparable with published data and comparison is given in Table 5.

Table 5. Specificity, sensitivity, positive (PPV) and negative (NPV) predictive values in previous studies compared with this study.

Study	Sample size	Sensitivity	Specificity	PPV	NPV
Our study (Sri Lanka)	152	84.05%	86.74%	84.05%	86.74%
J Ayub Med Coll Abbottabad 2006[7] (Pakistan)	125	98%	70%	91%	93%
Indian Journal of Pathology and Microbiology [11] 1996 (India)	128	92.3%	100%	92.3%	98.9%
Ann R Coll Surg Eng 2000 [12] (UK)	239	86.8%	67.0%	87.5%	65.5%
Clin Endocrinol (Oxf) 1999[13] (Czech. Republic)	2492	86%	74%	34%	97%
J Surgical Oncology 1995[14] (India)	100	76.5.%	95.9.%	86.7%	92.2%

According to the above results of the Asian, English and European studies the sensitivity, specificity, positive and negative predictive values of FNAC in detecting thyroid diseases ranges from 84-98%, 67-100%, 34-92%, and 65-94% respectively. The determinant factors for such a wide range could be the methodological differences, the technique of aspiration, preparation of smears, the nature of the nodule, condition of the sample and experience of the reporting pathologist. In the current study, all the smears were fixed in alcohol and stained with Haematoxylin and Eosin. Aspiration and interpretation were both done by histopathologists. In some comparable studies, air-dried smears were also prepared and cytological interpretation was carried out by cytopathologists, who are specialized in cytodiagnosis.

Discussion

There were 11(7.2%) false positives in the current study (Table 5, Figure 3). This rate is higher than the reported false positive rates ranging from 0-4%. The factors attributing to these could be poor aspiration technique and smear preparation technique, poorly localized lesions, inadequate clinical history and investigation findings, coexisting dual pathology, non-compliance of the patients, and differences in interpretation by the pathologists.

The majority of false positive cases (10/11) were due to misinterpretation of thyroiditis and colloid goiters as follicular neoplasms. This is a diagnostic pitfall where long-standing multinodular goiter or thyroiditis, exhibit areas of follicular hyperplasia, if sampled, can mimic a follicular neoplasm. There was one (1/11) false positive FNAC diagnosis of papillary carcinoma for autoimmune thyroiditis. This may be due to the overlap of cytological features observed in thyroiditis and papillary carcinoma.

False negative rate was 11(7.2%) in the current study, which is slightly higher than the highest reported incidence of 6%. The majority of these were follicular neoplasms (8/11) which were misinterpreted as colloid nodules. There were three (3/11) follicular carcinomas diagnosed as colloid nodules. This is expected with small thyroid nodules where the aspiration, which is a blind procedure, may not be representative of the lesion and may contain material from the surrounding non-neoplastic colloid nodules. This problem can be overcome by using ultrasound guided needle aspiration, which will be more representative of the lesion.

Cytological diagnosis of follicular adenoma versus carcinoma is not possible with fine needle aspiration and diagnosis is dependent on histological assessment for capsular or vascular invasion. In some studies follicular lesions were excluded from the calculation where this group was included in the neoplastic group. In this study, both follicular adenoma and follicular carcinoma were included in the follicular neoplasm category with a sensitivity of 68.18% and a positive predictive value of 65.21%.

More than 85% of specificity has been shown in diagnosing colloid goiters, thyroiditis, multinodular goiter, follicular neoplasm, and papillary carcinoma.
Positive predictive value for multinodular goiter (50%) and follicular neoplasm (65.21%) are quite low compared with other thyroid conditions. In colloid goiter there are small and large follicles so when only small follicles are aspirated it shows a vague follicular configuration mimicking follicular neoplasm. Low positive predictive value of multinodular goiter may be due to low prevalence of the disease in the sample. Negative predictive values for colloid goiter, thyroiditis, multinodular goiter, follicular neoplasm, and papillary carcinoma are more than 85%.

Limitations

There were 11 false negative cases, the majority of cases being due to failure to differentiate colloid goiter from follicular neoplasm. This is expected with small thyroid nodules where the aspiration, which is a blind procedure, may not be representative of the lesion and may contain material from the surrounding non-neoplastic areas. This problem can be overcome by using ultrasound guided needle aspiration, which will have a more representative cell yield.
There were 11 false positive cases in our study. This was mainly due to misinterpretation of thyroiditis and colloid goiter as a follicular neoplasm.
Cytological diagnosis of follicular adenoma versus carcinoma is not possible with fine needle aspiration and diagnosis is dependent on histological assessment for capsular or vascular invasion. In some studies follicular lesions were excluded from the calculation where this group was included in the neoplastic group. In our research we included both follicular adenoma and follicular carcinoma in the neoplastic group.

Conclusion and Recommendations

FNAC has an acceptable validity in the diagnosis of thyroid diseases by means of high specificity (86.74%), sensitivity (84.05%), positive predictive value (84.05%) and negative predictive value (86.74%).
Colloid goiter was found to be the commonest non-neoplastic condition in the current study.
Out of the neoplastic conditions, follicular neoplasms were the commonest followed by papillary carcinoma.

From the current study, the following recommendations can be made to improve the sensitivity, specificity, negative and positive predictive values that determine the validity of the FNAC in the diagnosis of a thyroid disease in Sri Lanka.

- Adherence to recommended techniques.
- Ultrasound guided aspiration for sample collection in small, ill-defined nodules and in a dominant nodule of a multi nodular goiter.
- In instances, where the FNAC results are not satisfactory in the diagnosis of a particular diseases condition, use of other supplementary investigations such as radiology and thyroid autoantibody levels.
- In all instances, a proper clinical history and investigation findings should be provided to the reporting pathologist.
- Training courses and workshops in cytopathology to enhance knowledge and expertise of the pathologists and improve reproducibility, sensitivity and specificity of FNAC.

Acknowledgements

We express our sincere gratitude to Prof. S. Sivayogan, Prof. Kumudu Wejewardana, Dr. Sampatha Goonawardana and all other members of Community Medicine Department, Dr. Kamani Samarasinghe, Head Department of Pathology and Prof. Mohan De Silva, Consultant Surgeon/ Head, department of Surgery, for their cooperation.
Financial support for this grant was received from the IRQUE/CBR Grants 2006 (Grant Number: IRQUE/CBR/RG/ 2006/9).

References

1. Stewart BW, Kleihues P. World Cancer Report. Lyon: 2003. 257-60.
2. Cancer Incidence Data: Sri Lanka Year 2000. Cancer Registry. 6th Publication. Sri Lanka: National Cancer Control Programme; 2000. 11.
3. Orell RS, Gegary F. Shetretf GF, WalFes MN *et al*. Manual and atlas of fine needle aspiration cytology. 2nd ed. 96-124.
4. Ogilvie JB, Piatigorsky EJ, Clark OH. Current status of fine needle aspiration for thyroid nodules. *Adv Surg Rev.* 2006; 40: 223-38.
5. Serna de la Saravia C, Cuellar F, Saravio Day E, Harach HR. Accuracy of aspiration cytology in thyroid cancer: a study in 1 institution. *Acta Cytol*. 2006 Jul-Aug; 50(4):384-6.
6. Cheung YS, Poon CM, Mak SM, Suen MW, Leong HT. Fine-needle aspiration cytology of thyroid nodules - how well are we doing? *Hong Kong Med J.* 2007 Feb; 13(1):12-5.
7. Mahar SA, Husain A, Islam N. Fine needle aspiration cytology of thyroid nodule: diagnostic accuracy and pitfalls. *J Ayub Med Coll Abbottabad*. 2006 Oct-Dec; 18(4): 26-9.
8. Wu M, Burstein DE. Fine needle aspiration. *Cancer Invest Review.* 2004; 22(4):620-8.

9. Sangalli G, Serio G, Zampatti C, Bellotti M, Lomuscio G. Fine needle aspiration cytology of the thyroid: a comparison of 5469 cytological and final histological diagnoses. *Cytopathology*. 2006 Oct; 17(5):245-50.
10. Godinho-Matos L, Kocjan G, Kurtz A. Contribution of fine needle aspiration cytology to diagnosis and management of thyroid disease. *J Clin Pathol.* 1992 May; 45(5): 391-5.
11. Sirpal YM. Efficacy of fine needle aspiration cytology in the management of thyroid diseases. *Ind J Pathol Microbiol.* 1996 Jul; 39(3): 173-8.
12. Tabaqchali MA, Hanson JM, Johnson SJ, Wadhera V, Lennard TW, Proud G. Thyroid aspiration cytology/histology correlation study. *Ann R Coll Surg Eng.* 2000 May; 82(3): 149-55.
13. Cáp J, Ryska A, Rehorková P, Hovorková E, Kerekes Z, Pohnetalová D. Sensitivity and specificity of the fine needle aspiration biopsy of the thyroid: clinical point of view. *Clin Endocrinol (Oxf).* 1999 Oct; 51(4): 509-15.
14. Agrawal S. Diagnostic accuracy and role of fine needle aspiration cytology in management of thyroid nodules. *J Surg Oncol*. 1995 Mar; 58(3): 168-72.