ORIGINAL ARTICLE

Fine Needle Aspiration (FNA) Cytology of the Thyroid: A Cyto-Histopathological Study of 361 Cases in Hospital Universiti Kebangsaan Malaysia

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ABSTRAK

Ketulan tiroid kerap ditemui tetapi neoplasma tiroid malignan jarang berlaku. Aspirasi sitologi jarum halus adalah kaedah diagnostik yang digunakan untuk menyaring pesakit tiroid yang memerlukan pembedahan. Kami mengkaji ketepatan diagnostik penggunaan aspirasi sitologi jarum halus sebagai kaedah modaliti diagnostik awal dalam penilaian klinikal ketulan tiroid. Sebanyak 2131 aspirasi jarum halus tiroid telah dilakukan di antara Januari 1995 dan Disember 2000 di Klinik FNA, Hospital Universiti Kebangsaan Malaysia (HUKM). Terdapat 441 (20.7%) kes-kes yang didapati tidak memuaskan untuk pemeriksaan sitologi manakala 1690 kes-kes yang selebihnya adalah memuaskan. Daripada jumlah ini, sebanyak 361 kes mempunyai diagnosis histopatologi. Korelasi sito-histopatologi dijalankan ke atas kes-kes ini. Keputusan kajian menunjukkan ketepatan diagnostik sebanyak 96.2% dengan kadar-kadar sensitiviti dan spesifisiti sebanyak 87.7% dan 98.4%. Nilai jangkaan positif adalah 93.4% dan nilai jangkaan negatif adalah 96.8%. Daripada keputusan kajian ini , kami merumuskan bahawa aspirasi jarum halus adalah kaedah diagnostik awal yang penting untuk penyiasatan ketulan tiroid.

Kata kunci: aspirasi jarum halus sitologi, ketulan tiroid, korelasi sito-histopatologikal, sensitiviti, spesifisiti

ABSTRACT

Thyroid nodules are common but thyroid malignancies are not. Fine needle aspiration (FNA) cytology is a diagnostic tool used to screen patients with thyroid nodules who require surgery. We study the diagnostic accuracy of FNA as the initial diagnostic modality in the clinical assessment of thyroid nodules. Between January 1995 until December 2000, 2131 FNA of thyroid nodules were performed. Four hundred and forty-one (20.7%) of these were unsatisfactory and 1690 (79.3%) cases were satisfactory for cytological evaluation. Histopathological diagnosis were available for 361 cases. Cyto-histopathological correlation was carried out for these cases. Our results showed a diagnostic accuracy of 96.2% with sensitivity and specificity rates of 87.7% and 98.4% res-

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pectively. Our positive predictive value is 93.4% and our negative predictive value is 96.8%. From this study, we conclude that fine needle aspiration is an important initial screening diagnostic tool for the investigation of thyroid nodules.

Key Words: Fine needle aspiration cytology (FNAC), thyroid nodules, cyto-histopathological correlation, sensitivity, specificity

INTRODUCTION

The incidence of thyroid nodules among adult population is between 4-7%, however, less than 5% of these nodules are malignant (Sclabas et al 2003). Few people die from thyroid carcinoma, on the other hand, thyroid surgery is associated with a number of risks like recurrent laryngeal nerve injury, hypoparathyroidism etc. Therefore, there is a need for an accurate test to screen the nodules that are likely to harbour malignancy and thus require operation while avoiding surgery of benign nodules.

Fine needle aspiration cytology was first described in the 1930s by Martin and Ellis, however it became widely accepted in the United States only in the late 1970s (Leonard et al 1997, Matesa et al 2002). Currently, fine needle aspiration (FNA) has emerged as one of the first-line diagnostic techniques in the evaluation of thyroid nodules. It is a simple, cost-effective and safe procedure with few complications. The main purpose of thyroid FNA is to select nodules that require surgery from those that do not. It can also be diagnostic for certain lesions such as classic nodular goiter, Hashimoto's thyroiditis, papillary carcinoma, medullary carcinoma, anaplastic carcinoma and metastatic carcinoma (Matesa et al 2002).

The aim of this study is to determine the diagnostic accuracy of FNA as the initial diagnostic modality in the evaluation of a thyroid nodule.

MATERIALS AND METHOD

A total of 2131 FNA thyroid were performed from January 1995 till December 2000 in Hospital Universiti Kebangsaan Malaysia (HUKM), a teaching hospital in Kuala Lumpur. Out of these, 441 FNAs were unsatisfactory for cytological evaluation. Of the remaining 1690 satisfactory samples, histopathological diagnoses were available for 361 cases.

Fine needle aspirations of palpable masses were performed by Pathology Registrars and Cytopathologists. Deep-seated lesions were performed by radiologists using ultrasound-guidance. The aspiration technique was the standard one described in the literature (Orell et al 2002). The thyroid mass was examined clinically to note its mobility, consistency and size. Cervical lymph nodes were palpated to detect enlargement. The skin was sterilized with alcohol. No local anaesthesia was used. Aspiration was performed under negative pressure using a disposable 23-gauge needle attached to a 20 ml syringe that was fitted to a Cameco syringe holder. Direct smears were prepared from the aspirated material. The procedure was repeated two to three times at different areas of the thyroid mass. In cases of cystic lesions, the cyst content was evacuated and smears were prepared from the cyst fluid. Reaspiration was performed if there was a remaining solid mass palpable.

At least two smears were fixed with alcohol and two air-dried. Alcohol-fixed smears were stained by the Papanicolaou method while the air-dried smears were stained by the May-Grunwald-Giemsa technique. All the smears were screened and reported by the Registrars undergoing cytopathology training and reviewed by the

Cyto-pathologist on-call. The cytologic smears were interpreted according to the criteria described by Orell (Orell et al 2002), Ramzy (Ramzy 2001) and Cibas (Cibas and Ducatman 2003).

Smears which contained no diagnostic cellular material or were heavily blood-stained are considered unsatisfactory for cytological evaluation. A repeat FNA was recommended in these cases.

The cytologic diagnosis was classified as benign (goitre, Graves disease, colloid cyst, and Hashimoto's thyroiditis), inconclusive (follicular neoplasms and Hurthle cell tumours) and malignant (papillary carcinoma, medullary carcinoma, anaplastic carcinoma, squamous cell carcinoma and non-Hodgkin lymphoma).

Subsequent to FNA, the histopathological reports of the cases that were operated on were traced from the histopathology files. The final histopathological diagnosis was then compared with the corresponding cytological diagnosis and cyto-histopathological correlations were established in 361 cases.

Statistical analysis

Cases with cytological diagnosis of follicular neoplasms and Hurthle cell tumours were regarded as inconclusive because it is not possible to differentiate between follicular adenoma (benign) from follicular carcinoma (malignant) based on cytological assessment. Hence, these cases were not included in the calculation for sensitivity, specificity, positive and negative predictive values and diagnostic accuracy. Unsatisfactory cases were also excluded from calculation.

True positives (TP) were defined as cases diagnosed as malignant on cytology which were histologically confirmed. False positives (FP) were those diagnosed as malignant on cytology that were benign on histology. True negatives (TN) were benign on both cytology and histology. False negatives (FN) were negative on cytology but positive for malignancy on histology. The diagnostic accuracy was calculated as:

(TP + TN) / (TP +FP + TN + FN)

RESULTS

There were 2131 FNA thyroid performed in HUKM from January 1995 till December 2000. Out of these, 441 (20.7%) were reported as unsatisfactory, thus leaving 1690 (79.3%) satisfactory cases for cytological evaluation. Histopathological diagnoses were available for 361 cases. Correlation between cytological and histopathological diagnosis was done on these cases.

From the 361 cases, 253 (70.1%) were classified as benign, 61(16.9%) malignant and 47 (13.0%) were inconclusive on cytology. These results are shown in Table 1.

The detail of cytological and the corresponding histopathological diagnosis

Table 1. Results of FNA cytology

No.	FNA Classification	FNA diagnosis	No of cases (%)	Total no of cases (%)
1.	Positive for malignancy	Papillary carcinoma	47 (13.0%)	61 (16.9%)
		Anaplastic carcinoma	11(5%)	
		Non-Hodgkin lymphoma	1(0.3%)	
		Medullary carcinoma	1(0.3%)	
		Squamous cell carcinoma	1(0.3%)	
2.	Negative for malignancy (Benign)	Goitre	233 (64.5%)	253 (70.1%)
		Cyst	18(5.0%)	
		Graves disease	1(0.3%)	
		Hashimoto's thyroiditis	1(0.3%)	
3	Inconclusive (follicular lesion)	Follicular neoplasm	41(11.3%)	47(13.0%)
		Hurthle cell tumour	6(1.7%)	
	Total		361(100%)	361

Table 2. Results of FNA cytology with subsequent histopathological diagnosis.

Histology Cytology	N	Goitre	Cyst	Graves	HT	FA	HCT	FC	PTC	MC	AC	SCC	NHL	**Total**
Goitre	2	216	1	-	3	4	-	1	6	-	-	-	-	233
Cyst	-	5	8	-	2	1	1	-	1	-	-	-	-	18
Graves	-	-	-	1	-	-	-	-	-	-	-	-	-	1
Hashimoto's thyroiditis	-	-	-	-	1	-	-	-	-	-	-	-	-	1
Follicular neoplasm	-	4	-	-	-	31	-	5	1	-	-	-	-	41
Hurthle cell tumour	-	-	-	-	2	-	4	-	-	-	-	-	-	6
Papillary carcinoma	-	3	-	-	-	1	-	2	41	-	-	-	-	47
Medullary carcinoma	-	-	-	-	-	-	-	-	-	1	-	-	-	1
Anaplastic carcinoma	-	-	-	-	-	-	-	-	-	-	11	-	-	11
Squamous cell carcinoma	-	-	-	-	-	-	-	-	-	-	-	1	-	1
Non-Hodgkin lymphoma	-	-	-	-	-	-	-	-	-	-	-	-	1	1
TOTAL	2	228	9	1	8	37	5	8	49	1	11	1	1	**361**

N: Normal
HT: Hashimoto's thyroiditis
FA: Follicular adenoma
HCT: Hurthle cell tumour
FC: Follicular carcinoma
PTC: Papillary carcinoma
MC: Medullary carcinoma
AC: Anaplastic carcinoma
SCC: Squamous cell carcinoma
NHL: Non-Hodgkin lymphoma

is shown in Table 2. Histopathological examination confirmed the benign lesions in 245 (96.8%) of the 253 cytologically benign cases, which represent true negative cases. In these cases, FNA cytology correctly diagnosed 216 (92.7%) of the 233 goitres. There were 18 cases diagnosed as cyst on cytology. Out of these, subsequent histology revealed eight cysts, five goitres, two Hashimoto's thyroiditis, one Hurthle cell tumour, one follicular adenoma and one papillary carcinoma.

There were eight (3.2%) false negative cases which included six papillary carcinoma cytologically diagnosed as goitre, one papillary carcinoma diagnosed as cyst and one follicular carcinoma which was interpreted as goitre on cytology.

Of the 61 patients diagnosed as malignant on FNA cytology, 57 (93.4%) were confirmed malignant on histopathological examination, thus were true positives (41 papillary carcinoma, one follicular carcinoma, one medullary carcinoma, 11 anaplastic carcinoma, one squamous cell carcinoma and one non-Hodgkin lymphoma). There were four (6.6%) false positive cases. These cases were cytologically diagnosed as papillary carcinoma from which three were histologically diagnosed as goitre and one as follicular adenoma. Table 2 depicts the detail of cytological and the corresponding histopathological diagnosis. Table 3 summarises the cytological and corresponding histopathological diagnosis.

We classified 47 cases as inconclusive (41 follicular neoplasms and six Hurthle cell tumours) because it is not possible to differentiate between follicular adenoma and follicular carcinoma based on cyto-

Table 3. Summary of cyto-histopathological correlation of all 361 cases

Cytology	Histology		
	Benign	**Malignant**	**Total**
Benign	245 (96.8%) (TN=84.4%)	8 (3.2%) (FN=11.2%)	253 (70.1%)
Malignant	4 (6.5%) (FP=1.4%)	57 (93.4%) (TP=80.3%)	61 (16.9%)
Inconclusive	41 (87.2%)	6 (12.8%)	47 (13.0%)
Total	290 (80.3%)	71 (19.7%)	361 (100%)

TN: True negative FN: False negative
TP: True positive FP: False positive

Table 4. Calculations of diagnostic accuracy, sensitivity, specificity, negative and positive predictive values

Analysis	
Accuracy	$= \frac{TP + TN}{TP + TN + FP + FN}$ $= \frac{57 + 245}{57 + 245 + 4 + 8} x100$ $= 96.2\%$
Sensitivity	$= \frac{TP}{TP + FN}$ $= \frac{57}{57 + 8} x100$ $= 87.7\%$
Specificity	$= \frac{TN}{TN + FP}$ $= \frac{245}{245 + 4} x100$ $= 98.4\%$
Positive Predictive Value	$= \frac{TP}{TP + FP}$ $= \frac{57}{57 + 4} x100$ $= 93.4\%$
Negative Predictive Value	$= \frac{TN}{TN + FN}$ $= \frac{245}{245 + 8} x100$ $= 96.8\%$

TN: True negative FN: False negative
TP: True positive FP: False positive

logical assessment alone. The same criteria applies for Hurthle cell adenoma and carcinoma. Of the 41 follicular neoplasms, six were malignant on histology (five follicular carcinoma and one papillary carcinoma) while 31 were confirmed follicular adenoma and four goitres. Two of the six Hurthle cell tumours diagnosed on cytology turned out to be Hashimoto's thyroiditis on subsequent histopathological examination, and in the other four, the diagnosis of Hurthle cell tumour was correctly made.

From the data, our sensitivity rate for thyroid FNA is 87.7% and our specificity rate is 98.4%. Our positive predictive value is 93.4% and our negative predictive value is 96.8%. The diagnostic accuracy of FNA thyroid at our center is 96.2%. The formula used and the calculations are shown in Table 4.

DISCUSSION

For thyroid FNA cytology to be clinically useful, a satisfactory sample must be obtained. Smears from thyroid aspirates are considered satisfactory when the material is representative of the lesion, adequate in quantity and the cyto-preparation is excellent. Our unsatisfactory rate is 20.7% which is on the high side compared with other previous studies which reported unsatisfactory rates between 0 to 25% (Ramachandra et al 1995). This could be attributed to the aspirations being performed by Trainee Registrars, who had limited experience during the initial part of their training. The quality of the smears usually improved as each student completed his or her three months cytology training. At our centre, a repeat FNA will be done for cases classified as inadequate. According to the Papanicolaou Society of Cytopathology Task Force, an acceptable rate of inadequate smears should be kept less than 15% (The Papanicolaou Society of Cytopathology Task Force 1996).

In this study, we obtained a sensitivity rate of 87.7% and a specificity rate of 98.4%, which gives a diagnostic accuracy

of 96.2%. Our results are comparable with several other studies which reported sensitivity rates between 65% to 98%, specificity rates between 72% to 100% (Sanggali et al 2006) and diagnostic accuracy rates between 70% to 90% (Vojvodich et al. 1994). The sensitivity, specificity and diagnostic accuracy depend on the experience of the person performing the aspiration and the cytopathologist interpreting the smear, the statistical method employed and whether the follicular lesions were included or not; and if they were included whether they were classified as benign or malignant. In our analysis, we did not include the cases classified as inconclusive which represent follicular neoplasms and Hurthle cell tumours, because the objective of this study is to calculate the diagnostic accuracy of fine needle aspiration cytology in thyroid lesions at our centre rather than its impact on clinical management.

Our false negative rate is 3.2%. This figure is in agreement with the other studies which reported false negative rates between 1-11% (Sanggali et al 2006). False negative rate is a concern because a missed malignant lesion will result in dire consequences for the patient. Review of these cases showed that most of them were due to sampling errors especially in the case of a cystic lesion where papillary carcinoma was missed. One case of follicular carcinoma was cytologically diagnosed as goitre (Table 2). This was also considered as sampling error because the relative abundance of cellular material lacking in microfollicular pattern in a background of moderate amount of colloid as seen in this case would inevitably render a cytologic diagnosis of hyperplastic goitre. After all, one has to make diagnosis based on the available cytologic material and according to standard criteria. We feel that in these cases, radiology-guided fine needle aspiration may reduce this problem in some of these cases. Clinical correlation is strongly recommended in cases where suspicion of malignancy is high but cytologically reported as benign. For these cases, we recommend a repeat aspiration or radiologically-guided aspiration. Therefore, communication between the clinician and the cytopathologist is extremely important.

There were four false positive cases giving a rate of 6.6%. The reported false positive rates in the literature vary from 0.3% to 10% (Suresh et al 1995). This was not considered a major problem because these patients would have been operated based on other clinical parameters. Three goitres were cytologically diagnosed as papillary carcinoma of the thyroid. Review of these cases showed that these were due to interpretative errors. In these cases, diagnosis of papillary carcinoma of the thyroid was offered due to hypercellularity of the specimens together with scant amount of colloid and the occasional presence of longitudinal grooves accompanied by intranuclear pseudoinclusion-like features. The other false positive case was a follicular adenoma misdiagnosed as papillary carcinoma of the thyroid. Because longitudinal grooves and intranuclear pseudoinclusions are occasionally observed in other thyroid lesions, Cibas (Cibas et al 2003) stressed the significance of pale, powdery chromatin pattern in papillary carcinoma (Figure 1) as a helpful distinguishing feature from the coarse chromatin pattern seen in follicular lesions (Figure 2). Awareness by the cytopathologists of this problem should reduce this particular diagnostic error in future.

Finally, even though we excluded the inconclusive cases from our calculations, it was interesting to note that we correctly assigned 36 (87.8%) out of 41 cases diagnosed as follicular neoplasms. Histological diagnosis confirmed 31 cases of follicular adenoma and five cases of follicular carcinoma. Despite the extensive work done on separating follicular adenoma and carcinoma on cytological basis, only marginal success has been achieved. Molecular technique is another potential area which may help resolve this problem

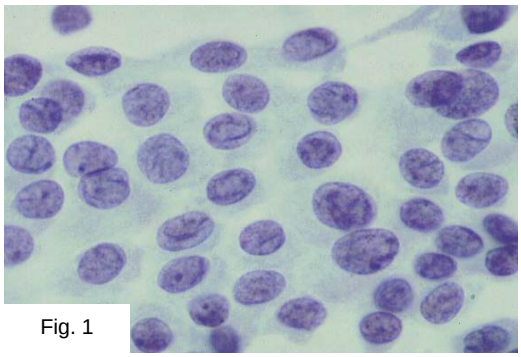

Fig. 1

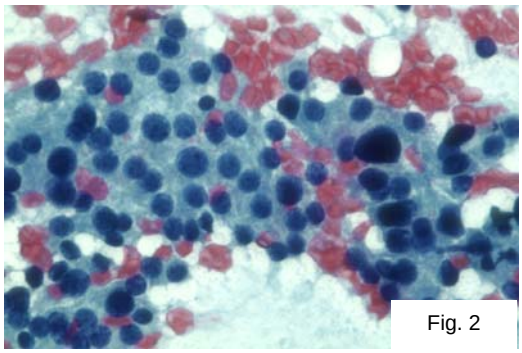

Fig. 2

Figure 1: Papillary carcinoma. Pale and powdery nuclear chromatin with longitudinal grooves. (Papanicolaou stain, 400X)

Figure 2: Follicular neoplasm displaying coarse chromatin pattern. (Papanicolaou stain, 400 X)

in future. Molecules like CD44v6 and Galectin 3 seem to be promising markers to detect neoplastic thyroid epithelial cells (Matesa et al 2002, Inohara et al 1994, Ermac et al 1995). However, more work and results are needed before they can be routinely used clinically. One of the follicular neoplasms turned out to be a follicular variant of papillary carcinoma of the thyroid. This mistake is not common due to the presence of overlapping follicular and papillary features. Careful assessment of the nuclear cytological features is important to avoid future mistakes in diagnosis of this variant.

In conclusion, results of our study showed that our sensitivity, specificity and diagnostic accuracy were high, thus confirming the important role of fine needle aspiration cytology as the initial diagnostic utility in the management of thyroid nodules. Sampling error was the major cause of our false negativity, which may be reduced by incorporating the other clinical parameters as index of suspicion of malignancy and utilizing radiology-guided aspiration.

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