ORIGINAL ARTICLE

Fine-needle aspiration cytology of thyroid nodules—how well are we doing?

YS Cheung 張宇新
CM Poon 潘志明
SM Mak 麥兆銘
Michael WM Suen 孫宏明
HT Leong 梁慶達

Objectives To review the accuracy of fine-needle aspiration cytology in diagnosing non-toxic thyroid nodules and determine what factors are predictive of malignancy in patients with indeterminate cytology results.

Design Retrospective study.

Setting Regional hospital, Hong Kong.

Patients Patients with non-toxic thyroid nodules undergoing thyroidectomy from December 1999 to December 2003.

Main outcome measures Sensitivity, specificity, positive and negative predictive value of fine-needle aspiration cytology, predictive factors for malignancy in patients with indeterminate fine-needle aspiration cytology results.

Results The sensitivity, specificity, positive predictive value, and negative predictive value of fine-needle aspiration cytology were 54%, 100%, 100%, and 75% respectively. For the 92 patients with fine-needle aspiration cytology reported as 'indeterminate for malignancy', aspiration cytology subgroup (P=0.005) and age (P=0.001) were significant risk factors for diagnosing malignancy.

Conclusions Fine-needle aspiration cytology has high positive predictive value for thyroid cancer, enabling us to 'rule-in' malignant lesions with confidence. Among those with indeterminate fine-needle aspiration cytology, atypical cell lesions and age greater than 40 years conferred increased risk of malignancy.

Introduction

Patients with non-toxic nodular goitre very commonly present to surgeons. The prevalence of patients with thyroid nodules ranges from 4 to 25%,[1-3] although only 5 to 10% are estimated to have malignant nodules.[1,2] It is important to differentiate between benign and malignant thyroid nodules, so as to avoid unnecessary surgery. Fine-needle aspiration cytology (FNAC) is recommended as the initial diagnostic test for such patients, because of its simplicity and reliability.[4-6] Moreover, FNAC has been shown to reduce the percentage of patients requiring thyroidectomy whilst doubling the yield of carcinoma in operated patients.[5,7] Thus, FNAC findings play a vital role in selecting patients for surgery, and hence, its accuracy is very important in patient management.

We therefore performed this study to review the accuracy of FNAC in diagnosing non-toxic thyroid nodules in our unit. In patients with indeterminate FNAC findings, possible risk factors of malignancy were also analysed.

Methods

We undertook a retrospective, systematic review of pathology records of all patients who underwent thyroidectomy at our regional hospital from December 1999 to December 2003 inclusive. Patients having a non-toxic thyroid nodule and preoperative FNAC were selected and their demographic data, size of lesion, FNAC and histology results were analysed.

Cytology results were categorised into four groups based on the original submitted report: positive for malignancy, negative for malignancy, indeterminate for malignancy, and inadequate sampling.[8] Indeterminate FNAC results were further subdivided into those reporting atypical

Key words
Biopsy, needle; Frozen sections; Predictive value of tests; Thyroid nodule

Hong Kong Med J 2007;13:12-5

North District Hospital, Po Kin Road, Sheung Shui, Hong Kong:
Department of Surgery
YS Cheung, MB, ChB, MRCS (Edin)
CM Poon, MB, BS, FRCS (Edin)
HT Leong, MB, BS, FRCS (Edin)
Department of Pathology
SM Mak, MB, ChB
MWM Suen, MB, ChB, FRCPath

Correspondence to: Dr HT Leong
E-mail: lamyn@ha.org.hk

cell, follicular cell, and Hurthle cell lesions. Fine-needle aspiration cytology samples were considered inadequate for diagnosis if there were fewer than six clusters of cells on each of two slides obtained from separate aspirates.[9]

We assessed the accuracy of FNAC findings by comparison to the final histology of the thyroidectomy specimen as the gold standard for the diagnosis. We excluded patients with a final histology showing follicular or Hurthle cell neoplasm from the analysis of accuracy, because it was not possible to diagnose the latter based on cytology.[5,6] Sensitivity, specificity, positive and negative predictive values of FNAC were calculated by defining papillary carcinoma, adenocarcinoma, and suspicion of papillary carcinoma as positive result. All other results were regarded as negative. For patients with indeterminate FNAC results, potential risk factors for malignancy were assessed by univariate and multivariate analysis, using a two-sided P value of <0.05 as significant.

Results

A total of 179 patients were identified; 142 (79%) were female and 37 (21%) male. The mean age at first presentation was 46 (standard deviation [SD], 13.5) years. The mean size of the dominant lesion was 2.7 cm (SD, 1.6 cm). Forty-eight (27%) of the patients had repeated FNAC before proceeding to surgery, among which the repeated FNAC sample was definitively recognised as malignant in two (4%) of these patients, but was reported as inadequate in seven (15%). Comparisons between FNAC results and histological diagnosis are shown in Table 1.

Including incidental papillary microcarcinoma, 59 (33%) of the patients had malignant lesions. There were 78 (44%) patients with follicular cell lesions, of which 14 (8%) were diagnosed as carcinoma. In 32 (18%) of the patients, FNAC was reported as inadequate sampling.

All patients with FNAC samples positive for malignancy were found to have thyroid cancer (Table 2). Twenty-three per cent of patients with indeterminate FNAC samples and 28% of those having samples reported as inadequate sampling were subsequently found to have carcinoma after thyroidectomy. After excluding follicular carcinoma (n=9), follicular adenoma (n=48), and Hurthle cell adenoma (n=4), the sensitivity, specificity, positive and negative predictive values of FNAC for diagnosing malignancy were 54%, 100%, 100%, and 75% respectively.

Predictive factors for malignancy were analysed in 92 (51%) of the patients with indeterminate FNAC results (Table 3). Patients with FNAC yielding atypical cells and those older than 40 years were significantly at risk of malignancy. In the logistic regression model, atypical cells conferred a 4-fold increased risk and age greater than 40 years a 7-fold increased risk.

甲狀腺結節細針穿刺細胞檢查準確嗎？

目的 檢討採用細針穿刺細胞檢查診斷無毒甲狀腺結節的準確度，確定在細胞學檢查結果不明確的情況下能預測結節是否惡性的因素。

設計 回顧研究。

安排 分區醫院，香港。

患者 1999年12月至2003年12月，發現有無毒甲狀腺結節並接受甲狀腺切除手術的病人。

主要結果測量 細針穿刺細胞檢查的敏感度、特異性、正負預測值，以及在細針穿刺細胞檢查結果不明確的情況下預測結節是否惡性的因素。

結果 細針穿刺細胞檢查的敏感度、特異性、正負預測值依次為54%、100%、100%，以及75%。92位細針穿刺細胞檢查結果為「惡性不確定」的病人中，穿刺細胞檢查小組（P=0.005）和年齡（P=0.001）是影響診斷結節是否惡性的主要風險因素。

結論 細針穿刺細胞檢查對甲狀腺癌的正預測值很高，讓醫療人員有信心決定癌病變的可能性。在細針穿刺細胞檢查結果不明確的病人中，出現非典型細胞病變和年齡40歲以上的，患癌的風險增加。

TABLE 1. Correlations of fine-needle aspiration cytology (FNAC) comparing to histology*

FNAC results	Histology, No.								
	PC	FC	AC	MC	IPMC	FA	HCA	BN	Total
PC	14	-	-	-	-	-	-	-	14
Suspicious of PC	12	1	-	-	-	-	-	-	13
AC	-	-	1	-	-	-	-	-	1
Atypical cells	5	1	-	-	1	2	-	3	12
Follicular cell lesion	6	4	-	1	3	38	3	23	78
Hurthle cell lesion	-	-	-	-	-	-	1	1	2
BN	-	-	-	-	1	1	-	25	27
Inadequate sampling	4	3	-	-	2	7	-	16	32
Total	**41**	**9**	**1**	**1**	**7**	**48**	**4**	**68**	**179**

* PC denotes papillary carcinoma, FC follicular carcinoma, AC adenocarcinoma, MC medullary carcinoma, IPMC incidental papillary microcarcinoma, FA follicular adenoma, HCA Hurthle cell adenoma, and BN other benign lesion

TABLE 2. Categorisation by fine-needle aspiration cytology (FNAC) compared to final histology

FNAC category	Histology, No. (%)	
	Malignant	Benign
Positive for malignancy (n=28)	28 (100)	0 (0)
Negative for malignancy (n=27)	1 (4)	26 (96)
Indeterminate (n=92)	21 (23)	71 (77)
Inadequate (n=32)	9 (28)	23 (72)
Total (n=179)	**59**	**120**

TABLE 3. Predictors of malignancy in indeterminate fine-needle aspiration cytology (FNAC)

	% of malignancy	Odds ratio (95% CI)	P value
Univariate analysis			
FNAC subgroup*		6.6 (1.8-23.8)	0.005
Atypical cells (n=7)	58%		
Follicular and Hurthle cell lesions (n=14)	18%		
Gender*		0.7 (0.2-2.5)	0.730
Female (n=17)	22%		
Male (n=4)	29%		
Age* (years)		9.8 (2.1-45.1)	0.001
≥40 (n=16)	35%		
<40 (n=5)	5%		
Multivariate analysis†			
FNAC subgroup—atypical cell		4.1 (1.1-15.8)	0.038
Age (≥40 years)		7.6 (1.6-36.2)	0.011

* Fisher's exact test
† Logistic regression

Discussion

Fine-needle aspiration cytology is a simple, safe, reliable, and cost-effective test for malignancy in thyroid nodules.[6] Diagnostic accuracy varies between different series (Table 4[3,5,10-12]) and depends on the method of data analysis.[5] Good aspiration technique and availability of experienced cytologists are of importance in achieving high diagnostic accuracy.[1,6,13]

In our series, the diagnostic accuracy of FNAC positive for malignancy was comparable to international figures.[3,5,10] A specificity and positive predictive value of 100% were achieved. We can 'rule in' a diagnosis of thyroid carcinoma with confidence. These patients should be treated with surgery.

For patients with FNAC negative for malignancy (Table 2), only one (4%) of them was found to have malignancy. Thus, most patients with an adequate FNAC sample diagnosed to have a benign lesion (without atypical cell, follicular cell, or Hurthle cell lesions) do not have a cancer. If they are not symptomatic, surgery could be avoided.

Although a positive FNAC result is very useful in selecting patients for surgery, a negative FNAC is sometimes inconclusive and poses diagnostic clinical challenge. Indeterminate FNAC findings were due to difficulty in differentiating benign follicular and Hurthle cell growths from their malignant counterparts.[5] The diagnosis of follicular and Hurthle cell carcinoma requires identification of capsular or vascular invasion, which is impossible with an FNAC specimen.[6] Ninety-two patients in our series belonged to this category, and 23% (n=21) of them were subsequently found to have malignancy. Patients having an FNAC diagnosis of atypical cell, follicular or Hurthle cell lesions should be advised to undergo surgery, as a significant proportion harbour malignancy.

Another limitation of FNAC is inadequate sampling, which gives rise to non-diagnostic results. Insufficient cellular material from cystic or haemorrhagic lesions, the experience of cytopathologists in performing aspirations, the numbers of punctures, and the technique of preparing smears all affect the rate of non-diagnostic results.[6] Use of ultrasound guidance was shown to decrease the proportion of non-diagnostic results as compared to freehand FNAC.[10,14] However, there was no change in the overall sensitivity or specificity. In our series, 18% (n=32) of the patients had inadequate sampling, which was comparable to other large series (Table 4). Together with the incidental findings of papillary microcarcinoma (n=7), they were the major factors contributed to the low sensitivity (54%) and negative predictive value (75%) encountered in our series.

Because of these limitations, various studies have tried to delineate the risk of malignancy when FNAC is inconclusive. Thus, sub-classification according to cytology results and age were shown to be predictive of malignancy.[8] In our series, age greater than 40 years and presence of atypical cells were the significant risk factors of detecting malignancy in patients with indeterminate

TABLE 4. Previously reported accuracy of malignancy categorisation by fine-needle aspiration cytology (FNAC)*

Series	No.	Malignant (%)	Suspicious (%)	Non-diagnostic (%)	FP (%)	FN (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gharib and Goellner,[5] 1993	3144	32	10	17	3	5	83	92	83	92
Chang et al,[3] 1997	662	25	22	7	8	10	65	98	92	95
Ogawa et al,[11] 2001	226	67	16	18	1	13	76	73	85	60
Sclabas et al,[12] 2003	240	43	42	5	4	4	71	98	96	82
Morgan et al,[10] 2003	253	13	29	14	26	46	55	74	70	67

* FP denotes false positive, FN false negative, PPV positive predictive value, and NPV negative predictive value

FNAC findings. Patients having these risk factors should receive early surgical intervention.

One limitation of our study was its retrospective design. Patients not undergoing an operation were not included, so that false-negative cases might have been missed. However, patients in our unit with indeterminate FNAC or inadequate sampling did receive surveillance in 3 to 6 months if they declined surgery. Thus, patients having malignant thyroid nodules should have been identified and treated during follow-up as the disease progresses, which minimise the bias in false-negative rate. This is evident by the fact that 31/59 (53%) of our malignant cases were diagnosed without a positive preoperative FNAC result (Table 2).

To conclude, FNAC in our unit has high specificity and positive predictive values for thyroid cancer. We were confident to 'rule-in' a malignant lesion by FNAC. However, its sensitivity is relatively low. We have to interpret negative results with caution, because some of thyroid nodules testing negative, nevertheless harbour malignancy. Among those with indeterminate FNAC results, atypical cell lesions and age greater than 40 years were conferred increased risk of malignancy, for whom early surgical intervention should be offered.

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