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Fine Needle Aspiration Cytology of Thyroid Nodules: Evaluation of Diagnostic Accuracy

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Abstract

Objective: The aim of this study was to evaluate the results of thyroid fine needle aspiration cytology (FNAC) and identify reasons for discrepancies between the cytological and histological diagnoses in our institution.
Materials and Methods: We evaluated the results of 1064 FNACs obtained from 737 patients, of which 98 underwent subsequent thyroid surgery.
Results: Histological analyses revealed that benign diagnoses based on FNAC were correct in 76 of the 80 benign cases (95%), with four cases being underdiagnosed (false negatives). Two of the four cases were due to incidental findings of papillary microcarcinomas. The third case was due to a cytologic sampling error and the fourth was due to cytologic underdiagnosis. Furthermore, malignant diagnoses based on FNAC were correct in 17 of the 18 malignant cases (94%), with one case being overdiagnosed (false positive) due to over-interpretation of Hürthle cells as carcinomatous cells. The accuracy, positive predictive value, and negative predictive value were 94.9%, 94.4%, and 95.0%, respectively.
Conclusion: Overall, FNAC is a sensitive and specific method for the preoperative screening of thyroid nodules. However, due to limitations under some specific circumstances, such as papillary microcarcinoma, bizarre Hürthle cells, follicular neoplasm and technical difficulty during the aspiration, the management of thyroid nodules must not only depend on the results of FNAC but should also be correlated with clinical findings before surgical intervention. (*Tzu Chi Med J* 2008;20(4):296–303)

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1. Introduction

The prevalence of thyroid nodules has been estimated to be as high as 25% or more in iodine-deficient regions, whereas only 4–7% of the population is estimated to have thyroid abnormalities in non-iodine-deficient areas (1). In Taiwan, the incidence of adult goiter is 19.4% in men, 33.6% in women, and 25%

in the total population [2]. Furthermore, it is estimated that only 5–10% of non-toxic thyroid nodules are malignant [3,4]. Thus, the main goal for clinicians is to distinguish between benign and malignant nodules in order to decrease the number of unnecessary thyroidectomies.

A number of researchers have demonstrated that physical examination, thyroid scintigraphy, thermography, X-ray techniques, thyroid hormone suppression, and ultrasonography are not reliable with respect to identifying neoplastic thyroid nodules. In contrast, thyroid fine needle aspiration cytology (FNAC) has been shown to be a simple, safe, reliable and cost-effective technique for detecting malignant nodules and has been purported to be the diagnostic method of choice in the initial approach to patients with thyroid nodules [5–7]. Since the introduction of FNAC, the total number of thyroid surgeries has markedly decreased [8]. However, in spite of its well recognized value, there are drawbacks to thyroid FNAC, including a high number of inadequate aspirates, the inability to reliably distinguish follicular adenoma from follicular carcinoma, and the possibility of false-negative and false-positive diagnoses [7,9–12].

The aim of this study was to evaluate the accuracy of thyroid FNAC and identify reasons for discrepancies between the cytological and histological diagnoses in our institution.

2. Materials and methods

From August 2003 through May 2007, a total of 1064 consecutive thyroid FNACs from 737 patients (111 male, 626 female) were conducted at the Buddhist Dalin Tzu Chi General Hospital in Chiayi, Taiwan, and included for evaluation in this study. In 190 cases, more than one (2–8 times) aspirate was performed due to various reasons, including inadequate specimen, routine follow-up, multiple nodules, and reconfirmation of cellular atypia or suggested malignancy. The mean age of the patients was 51.8 years (range, 13–92 years). Of the 737 patients, 98 (13.3%) subsequently underwent surgery.

Fine needle aspirations of the thyroid nodules were performed by one of four clinicians using 23-gauge needles attached to 5 or 10 mL disposable syringes using either the free-hand procedure or sonographic guidance according to each patient's clinical findings. For each aspiration, two to six alcohol-fixed and air-dried smears were prepared and stained using the methods of Papanicolaou and/or Liu as the clinicians preferred. A smear was considered satisfactory if it contained at least five to six groups of 10–15 well-preserved, well-visualized follicular cells [13]. Cystic lesions with numerous hemosiderin-laden macrophages and few or no follicular cells were regarded as satisfactory with a qualifier indicating that the interpretation was limited due to the paucity or lack of follicular cells [14].

Cytological diagnoses following FNAC were classified according to four groups as follows: (1) negative for malignancy; (2) cellular atypia; (3) suggestive of malignancy; and (4) malignant. Cytological specimens without evidence of cellular atypia or malignancy were classified as negative for malignancy. Aspirates displaying atypical cells with equivocal nature were included in the cellular atypia group. Smears exhibiting unequivocal or somewhat equivocal cytological pictures of malignancy were categorized in the malignant and suggestive of malignancy groups, respectively.

When comparing the cytological diagnosis with the definitive histological diagnosis of the 98 subjects who underwent surgery, the categories negative for malignancy and cellular atypia were collectively grouped as benign. Similarly, the suggestive of malignancy and malignant categories were collectively grouped as malignant. The cytological and histological diagnoses were evaluated for concordance (same diagnosis) and discordance (different diagnoses). Histological sections and cytological smears of the discrepant cases were reviewed to ascertain the reasons for the discordance.

Finally, the following parameters were calculated according to the standard criteria: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, false-positive rate (FPR), and false-negative rate (FNR) [15].

3. Results

Of the 1064 FNACs, 999 (93.9%) aspirates were classified as negative for malignancy, 40 (3.8%) as cellular atypia, 19 (1.8%) as suggestive of malignancy, and six (0.5%) as malignant (Table 1 and Fig. 1). Diagnoses in the negative for malignancy group included benign follicular cells in 426 aspirates, hemorrhagic cyst in 248 aspirates, nodular goiter in 213 aspirates, follicular lesions in 29 aspirates, thyroiditis in nine aspirates, as well as dissatisfaction due to inadequate cellularity or poorly fixed smears in 74 aspirates. Ninety-eight patients (13.3%) had undergone surgical intervention. The distribution of the 98 histopathological results and their correlation with the four cytological categories are shown in Tables 1 and 2. Of the 21 malignant cases identified by histopathology that underwent surgery, four were not diagnosed using FNAC. The cytohistologic correlation of the four false-negative cases and the reasons for the discrepancies are summarized in Table 3. Two of the four false-negative cases were due to incidental findings of papillary microcarcinomas. The other two cases were due to cytological sampling error and interpretation

Table 1 — Correlation between four cytologic categories and histopathologic results

Category of cytologic diagnosis	Number of cases based on FNAC	Number of cases undergoing surgery and diagnosis based on FNAC		
Negative for malignancy	999			71
		Nodular goiter with cystic degeneration	31	
		Nodular goiter	26	
		Follicular adenoma	5	
		Papillary microcarcinoma	2	
		Hürthle cell adenoma	2	
		Papillary carcinoma	2	
		Subacute thyroiditis	1	
		Psammomatous nodular hyperplasia	1	
		Autoimmune thyroiditis	1	
Cellular atypia	40			9
		Nodular goiter with cystic degeneration	3	
		Hürthle cell adenoma	2	
		Hashimoto's thyroiditis	2	
		Follicular adenoma	1	
		Subacute thyroiditis	1	
Suggestive of malignancy	19			14
		Papillary carcinoma	10	
		Follicular carcinoma	1	
		Angiosarcoma	1	
		Papillary microcarcinoma	1	
		Hashimoto's thyroiditis	1	
Malignant	6			4
		Papillary carcinoma	3	
		Hürthle cell carcinoma	1	
Total	1064			98

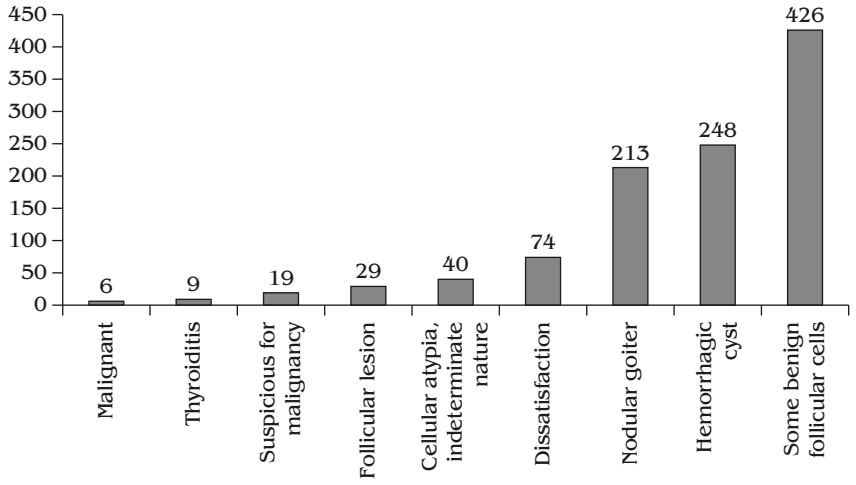

Fig. 1 — Distribution of cytologic diagnoses in 1064 FNACs.

Table 2 — Comparison of cytologic results to histopathologic results

FNAC results	Histologic results		
	Malignant	Benign	Total
Malignant*	17	1	18
Benign†	4	76	80
Total	21	77	98

*Malignant+suggestive of malignancy groups in FNACs; †negative for malignancy+cellular atypia groups in FNACs.

error, respectively. Furthermore, of the 77 histologically benign cases, one was misdiagnosed as malignant. This false-positive case was due to interpretation of Hashimoto's thyroiditis as carcinoma.

The group of cellular atypia included 40 cases in which nine (22.5%) subjects underwent thyroidectomy. Surgical diagnoses included three nodular goiters with hemorrhagic cystic degeneration, two Hürthle cell adenomas, two Hashimoto's thyroiditis, one follicular adenoma and one subacute thyroiditis. None in the nine surgical cases showed malignancy. Of the

Table 3 — Causes of discrepancies in the four false-negative cases based on histopathology

Case	Cytological diagnosis	Histological diagnosis	Discrepant causes
1	Nodular goiter	Papillary microcarcinoma (0.2 cm), nodular goiter	Incidental finding
2	Negative for malignant cell (some microfollicles)	Papillary carcinoma (1.2 cm)	Sampling error
3	Microfollicular lesion	Papillary carcinoma (2.5 cm), follicular variant, Hürthle cell adenoma, and nodular goiter	Cytologic underdiagnosis
4	Inadequate smear (bloody smear only)	Papillary microcarcinoma (0.7 cm), nodular goiter	Incidental finding

Table 4 — Comparison of the results of this study with other reported series published after 2000

Authors	Year	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	PPV (%)	NPV (%)	Accuracy (%)	Dissatisfaction (%)
Bakhos et al [16]	2000	93.0	96.0	8.0	4.0	–	–	88.0	7.0
Amrikachi et al [17]	2001	93.0	96.0	11.7	7.0	–	–	–	29.0
Morgan et al [18]	2003	55.0	73.7	26.3	45.8	70.0	67.4	67.2	14.0
Ko et al [11]	2003	78.4	98.2	1.8	21.5	99.0	66.3	84.4	–
Jogai et al [19]	2005	88.4	99.1	0.5	3.6	–	–	78.1	2.6
Cai et al [20]	2006	83.3	98.0	5.7	–	71.4	98.4	97.0	–
This study	2008	81.0	98.7	1.3	19.0	94.4	95.0	94.9	7.0

FPR = false-positive rate; FNR = false-negative rate; PPV = positive predictive value; NPV = negative predictive value; – = unknown data.

19 cases in the suggestive of malignancy group, 14 underwent surgery. Histological evaluation revealed 12 carcinomas and one angiosarcoma. Furthermore, one case in this group presented with Hashimoto's thyroiditis but no malignancy. Finally, of the six cases in the malignant group, four underwent surgery with histological evaluation revealing carcinomas in all four cases. The surgical rate of the cytological malignant group was 72.0%.

A total of 40 follicular lesions including 29 cases of them categorized as negative for malignancy and 11 cases as cellular atypia were diagnosed using FNAC with 12 (30.0%) of these subjects receiving surgical intervention. Histological diagnoses included three follicular adenomas, three Hürthle cell adenomas, two nodular goiters, two Hashimoto's thyroiditis, one follicular carcinoma, and one follicular variant of papillary carcinoma. The cytologic accuracy in diagnosing follicular neoplasm was roughly 58.3% (7/12).

Based on the above results, the following parameters were calculated: (1) sensitivity, 81% (17/21); (2) specificity, 98.7% (76/77); (3) FPR, 1.3% (1/77); (4) FNR, 19.0% (4/21); (5) PPV, 94.4% (17/18); (6) NPV, 95.0% (76/80); and (7) accuracy, 94.9% (93/98). In addition, the dissatisfaction rate was 7.0% (74/1064). Five of the 74 unsatisfactory cases underwent thyroidectomy. In these five cases, the histological results showed two nodular goiters with hemorrhagic cystic degeneration, one nodular goiter, and two nodular goiters with papillary microcarcinomas. These calculated parameters based on our results are compared in Table 4 with the data from six other studies published after 2000 [11,16–20].

4. Discussion

FNAC is an accurate preoperative screening method for the evaluation of thyroid nodules and helps to distinguish malignant nodules from benign nodules for the purpose of distinguishing patients in need of surgical intervention [21]. Overall, the current study confirms the predictive value of FNAC as a diagnostic tool. However, false-positive and false-negative cases remain. Although the 1996 guidelines for FNAC of thyroid nodules established that the aim of the procedure is to achieve a FNR and FPR less than 2% and 3%, respectively [14], these ideal goals have been difficult to achieve as evidenced by higher than ideal rates in several recent reports (Table 4). In our current study, the FPR was 1.3%, similar to that in other reported studies with FPR between 0.5% and 26.3%.

The one false positive based on FNAC in our current report was due to erroneous interpretation of the Hürthle cells in Hashimoto's thyroiditis as carcinomatous cells. Notably, these Hürthle cells exhibited enlarged hyperchromatic nuclei, prominent nucleoli, occasional nuclear grooves and an increased nuclear to cytoplasm ratio (Fig. 2). Hürthle cells (also referred to as Ashkenazy cells) are the result of metaplastic changes in the follicular cells, which are large, polygonal square shaped cells with abundant granular and polychromatic cytoplasm and hyperchromatic nuclei with prominent "cherry-pink" macronucleoli [22]. Using Liu's stain, the finely pink cytoplasmic granules are more prominent than in the Papanicolaou stain. Owing to occasional nuclear grooves and intranuclear pseudoinclusions in the Hürthle cells, they are easily misidentified as malignant cells. This error was also

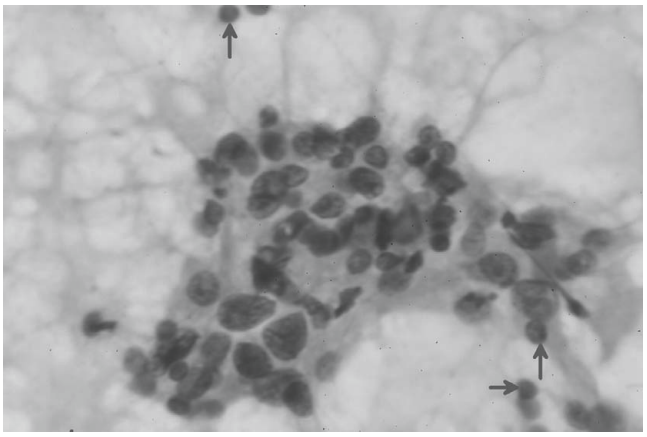

Fig. 2 — A cluster of Hürthle cells exhibiting enlarged hyperchromatic and pleomorphic nuclei, prominent nucleoli, and occasional nuclear grooves. Some lymphocytes (arrows) are also noted in the background. This Hashimoto's thyroiditis was misdiagnosed as suspicious for papillary carcinoma cytologically. (Papanicolaou stain, 1000×.)

reported by Ylagan et al in 2004 [23]. The presence of nuclear grooves among Hürthle cells in some cases of chronic lymphocytic thyroiditis and nodular hyperplasia was the most frequent cause of false-positive cases in their report [23]. Indeed, in our study, for five of the nine surgical cases in the cellular atypia group, cellular atypia of the related FNACs were due to Hürthle cells. Cytologically, it is difficult to assess the nature of Hürthle cells, especially when few cells are present and the fixation of the aspirate is less than optimal. Thus, when the nature of the Hürthle cells is uncertain, differential diagnoses should include normal variations in Hürthle cell morphology in thyroid follicles, nodular goiter with Hürthle cells, Hashimoto's thyroiditis, Hürthle cell adenoma/carcinoma, and Hürthle cell variant of papillary carcinoma. In addition, it should be known that the presence of a nuclear groove is not a specific feature of papillary carcinoma. A nuclear groove might also be present in Hashimoto's thyroiditis, follicular adenoma/carcinoma, and Hürthle cell neoplasm [23]. A case demonstrating some clusters of enlarged hyperchromatic nuclei of Hürthle cells with nuclear grooves was cytologically misdiagnosed as suggestive of papillary carcinoma in our study (Fig. 3). Finally, the surgical thyroid tissue presented a Hürthle cell adenoma with a large hemorrhagic cyst, which showed a ringed patch of angiosarcoma within an inner cystic wall.

The FNR in our study was 19.0%, which is similar to recent reports that showed FNRs between 3.6% and 45.8%. The causes of the four false-negative cases are summarized in Table 3. In two of the cases, histological evaluation revealed incidental findings of papillary microcarcinoma in addition to the main nodular goiters, which were the feature of interest when the FNACs were performed. In the other two cases, the false negatives were due to cytological sampling errors and cytological misdiagnosis of a follicular variant of papillary carcinoma as a microfollicular lesion. The prevalence of papillary microcarcinomas has been reported to be between 6.2% and 11.3% [24–26], with the exception of the highest reported prevalence rate of 35.6% reported in Finland [27]. Yamamoto et al noted that the incidence of papillary microcarcinomas is high in cases with adenomatous goiters [26]. This phenomenon was also present in our current study as well as in other studies [19,23]. However, it is extremely difficult to diagnose this small neoplasm (< 1 cm in diameter) using FNAC, especially when it is adjacent to a relatively large nodular goiter, which is usually the main target lesion in FNAC. Indeed, papillary microcarcinomas are generally incidental findings after surgical intervention of a clinically or ultrasonographically found nodule. Some authors do not consider these incidental microcarcinomas as true false-negative cases [28]. However, Yang et al pointed out that some of these microcarcinomas were clinically meaningful lesions because they might be multifocal and have lymph node metastases [29].

The follicular variant of papillary carcinoma is a pitfall in thyroid FNAC. Cytologically, it presents with hypercellularity with a prominent follicular pattern but no obvious papillae. Syncytial follicular cells, nuclear grooves, intranuclear pseudoinclusion and chewing gum colloid have been reported to be occasionally present in variable proportions [30]. However, none of these cytological pictures are specific, and may present in adenomatous goiters, follicular adenomas and follicular carcinomas at varying frequencies [19]. Leung et al revealed that the true nature of the histological variants of the papillary carcinoma cannot be predicted from the appearances of the FNAC [31]. Ylagan et al reported a cytologic follicular variant of papillary carcinoma, commenting that although the presence of a nuclear groove is nonspecific, it may be the only finding for this diagnosis [23]. In our present case, we histologically identified a 2.5-cm follicular variant of papillary carcinoma combined with a 1.1-cm Hürthle cell adenoma and a 1-cm nodular goiter. Cytologically, this papillary carcinoma demonstrated some microfollicles and Hürthle cells. Focally, follicular cells demonstrated moderately enlarged, hyperchromatic nuclei, scanty intranuclear pseudoinclusions and subtle nuclear grooves. We believe that aspects of these cytological features concealed a follicular variant of papillary carcinoma, rendering it difficult to make an accurate diagnosis cytologically.

One of the drawbacks of FNAC is its high unsatisfactory rate due to poor fixation and/or inadequate cellularity for interpretation. An experienced staff

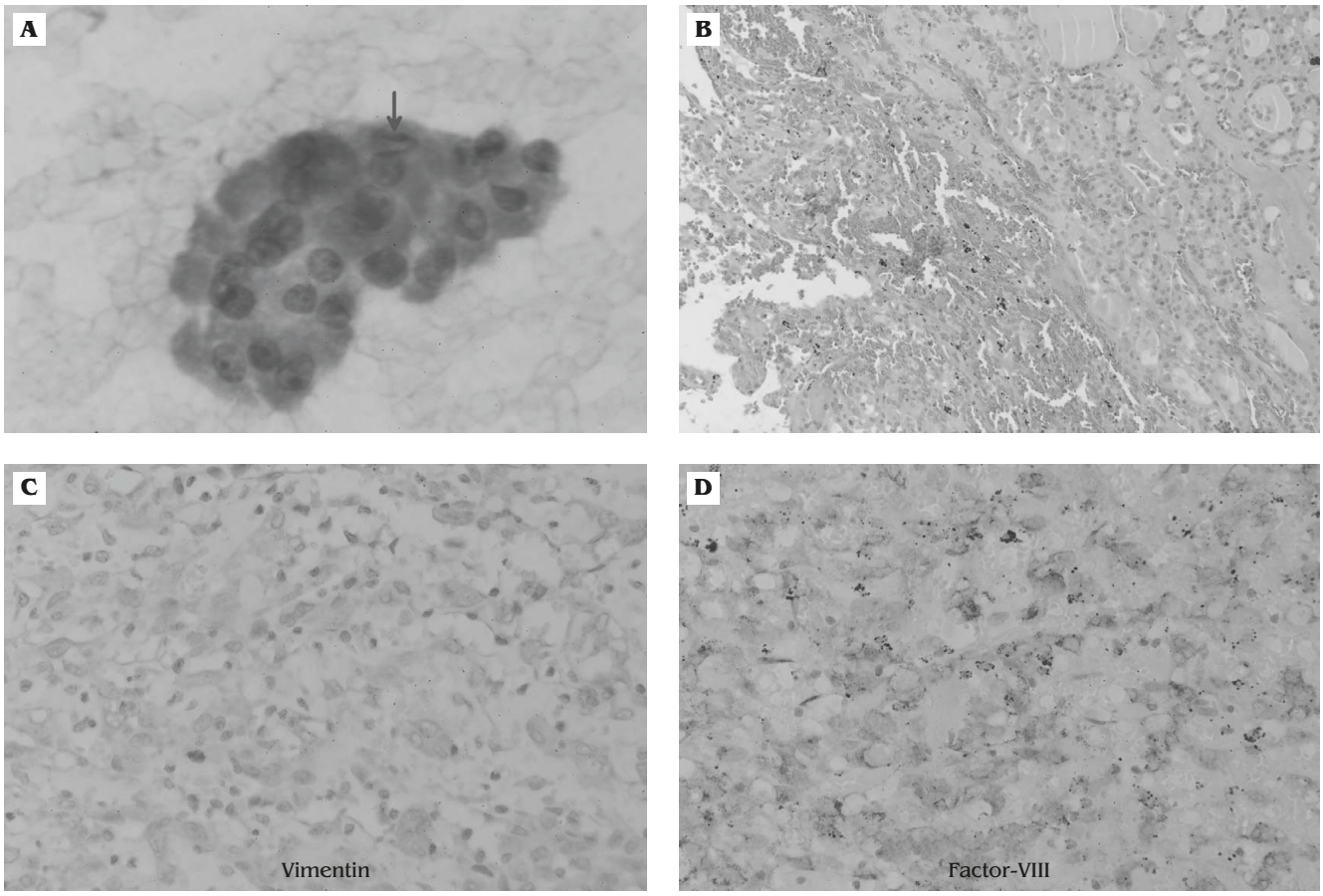

Fig. 3 — (A) A cluster of Hürthle cells exhibiting enlarged overlapping and irregular-sized nuclei with obvious nucleoli and nuclear grooves (arrow). These were cytologically diagnosed as suspicious for papillary carcinoma (Papanicolaou stain, 1000×). (B) However, the finally histologic evaluation revealed an angiosarcoma arising in a Hürthle cell adenoma. This picture showed the Hürthle cell adenoma (right upper part) with a central angiosarcoma (left lower part, hematoxylin & eosin, 200×). Immunohistochemical staining for angiosarcomatous cells shows positive staining for: (C) vimentin (400×); and (D) factor-VIII (400×).

can lower the poor fixation rate. The acceptable inadequate rate is less than 15% [14]. However, an inadequate smear might be a result of thyroid nodular character or inadequate sampling. Sclerotic, calcified or large cystic nodules are difficult to aspirate [10]. A sonographically guided aspirate could improve specimen acquisition [20,32]. The unsatisfactory rate in the current study was 7% and consistent with that reported in other recent studies, which range between 2.6% and 29.0% (Table 4). However, in five of the unsatisfactory cases that underwent surgery in the current study, two exhibited nodular goiters with papillary microcarcinomas. Although these malignancies were incidental findings, this highlights the need to re-aspirate all unsatisfactory samples before making definitive diagnoses [18,23,33]. Indeed, it is important to educate clinicians that an unsatisfactory smear does not equal a negative smear.

The other major drawback of FNAC is the lack of reliability with respect to distinguishing follicular adenoma from follicular carcinoma [7,34,35]. The reason for this is that the diagnosis of each entity is based on histological criteria, i.e., vascular and/or capsular invasion. FNAC cannot provide this information. The intraoperative frozen section is also handicapped in these cases because the histological diagnosis of follicular carcinoma often requires multiple sections with good preservation of morphology, which are not available in the frozen state. In addition, owing to the various overlapping cytological features, the differential diagnoses of cytological follicular patterns should include adenomatous nodule, follicular adenoma/carcinoma, and follicular variant of papillary carcinoma [19]. The results of our study are similar to previously reported results. Twelve of 40 subjects with cytologically identified follicular lesions underwent thyroidectomy, revealing three follicular adenomas, one follicular carcinoma, three Hürthle cell adenomas, two nodular goiters with hemorrhagic cystic degeneration, and one follicular variant of papillary carcinoma. In addition, two cases of Hashimoto's thyroiditis also showed follicular lesions cytologically with subtle

Hürthle cells and lymphocytic background, which were misinterpreted as naked follicular nuclei. Although follicular neoplasm is the handicap of FNAC, clinical information may complement this finding in some situations. A cytological follicular lesion associated with age >40 years, size >3 cm, and male gender might increase the risk of malignancy and should be more aggressively treated (12). However, in our study, only one 4.7-cm follicular carcinoma was histologically diagnosed in a 70-year-old female.

In this study, the accuracy, PPV, and NPV were 94.9%, 94.4%, and 95.0%, respectively. The data were similar to those in recent reports (Table 4), demonstrating that thyroid FNAC is a reliable screening test and also a valuable method of distinguishing neoplastic from non-neoplastic nodules preoperatively. However, owing to some limitations of FNAC as discussed above, it is recommended that surgical indications must not depend solely on cytology. Indeed, the results of medical history, physical examination, laboratory tests, and ultrasonography should also be evaluated simultaneously.

In conclusion, thyroid FNAC is a sensitive and specific method for screening thyroid nodules. However, owing to stationary limitations, such as the inability to reliably distinguish follicular adenoma from follicular carcinoma, difficulties in detecting papillary microcarcinomas, probability of over-interpreting Hürthle cells as carcinomatous cells and some technical difficulties and errors, the management of thyroid nodules must not depend only on FNAC. Correlating the results of FNACs with clinical findings is a must before surgical intervention is suggested in selected patients.

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