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## **Fine needle aspiration of follicular lesions of the thyroid: Cytohistologic correlation and accuracy at Gajraula region, Uttar Pradesh**

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**Abstract**--Background: Fine needle aspiration (FNA) is a reliable method in the initial assessment of thyroid nodules. This study evaluated the accuracy of fine needle aspiration cytology (FNAC) in cases of follicular neoplasm (FN) on the basis of histologic diagnosis, and reviewed the cytologic findings of FN according to the FNAC. Method: Among the 100 cases diagnosed with thyroid Follicular Neoplasm by FNAC during the 3 year period from October 2020 to September 2022, 54 cases that had undergone thyroid surgery were available for review. Cytologic diagnosis was compared with the histologic diagnosis of each case. Results: Among the 54 cases with a cytologic diagnosis of thyroid FN, histologic diagnosis was as follows: 32 follicular adenomas (59.3%), 4 Hurthle cell adenomas (7.4%), 2 follicular carcinomas (3.7%), 10 nodular goitres (18.5%), 2 papillary carcinomas (3.7%), and 1 Hashimoto's thyroiditis (3.7%), resulting in a diagnostic accuracy of FNAC for thyroid FN of 70.4%. Conclusion: This study shows that FNAC for thyroid FN is a useful primary screening method because when FN is diagnosed by FNAC, the rate of FN histological diagnosis is relatively high and however, adequate sampling and experience is a prerequisite for this procedure.

**Keywords**--thyroid gland, follicular neoplasm, fine needle, aspiration cytology.

## Introduction

Fine needle aspiration (FNA) has been widely accepted as an initial step in the management of thyroid nodules. Recently, as the use of ultrasonographic examination has increased, the possibility of incidental findings of thyroid nodules has also increased. The fine needle aspiration cytology (FNAC) of the thyroid gland is an important and definitive method for the diagnosis of thyroid nodules.<sup>1,2</sup> Follicular neoplasm (FN) and Hurthle cell neoplasm (HCN) are relatively rare diseases and their cytologic diagnosis is difficult when compared with papillary carcinoma (PC) which shows a cytologic accuracy of more than 90%. In addition, cytologic differentiation between benign and malignant tumors is not possible in FN and HCN cases. It is relied upon to distinguish benign from neoplastic/malignant thyroid nodules, thus, influencing therapeutic decisions.<sup>3,4</sup> However, the diagnostic efficacy of FNA declines sharply in the diagnosis of follicular patterned lesions of thyroid, i.e. separating hyperplastic/adenomatoid nodule, follicular adenoma (FA), follicular carcinoma (FCA) and follicular variant of papillary carcinoma (FVPTC).<sup>5,6</sup> Most of these cases are diagnosed as follicular lesion/neoplasm and surgical excision is recommended for definite diagnosis on histopathologic examination.<sup>7,8</sup> According to the guidelines for the treatment of thyroid nodules, surgery is recommended for patients when FN or HCN is diagnosed by FNAC because the possibility of malignancy in this case is not known until the histologic diagnosis is made from the lobectomy or total thyroidectomy specimen.<sup>1</sup> In contrast, guidelines for the treatment of PCs are relatively well established according to the categories of cytologic diagnosis. FN and HCN are still rare FNAC findings. Follicular carcinoma (FC) comprises approximately 5% of thyroid cancers,<sup>9</sup> and because the number of FN cases is limited and FC cannot be distinguished from benign follicular adenoma (FA) on the basis of cytologic findings, describing FN cytologically in an ambiguous manner may be inevitable. Therefore, more cytologic information regarding FN and HCN are required not only for the cytologic diagnosis but also for the development of appropriate treatment guidelines. In this study we evaluated the FNAC accuracy in FN cases based on the histologic diagnosis and investigated the cytologic findings to increase the probability of a correct cytologic FN diagnosis.

## Materials and Method

At Venkateshwar Institute of Medical Sciences (VIMS), Gajraula, 100 cases that had been diagnosed with thyroid FN by FNAC during the 3 year period from October 2020 to September 2022, 54 cases that underwent thyroid surgery were available for review. FNAC was performed under ultrasonographic guidance in all cases. The FNA was performed using a 25 gauge needle attached to a 10ml syringe. On average, 2 passes were made in each nodule, resulting in two air-dried and two alcohol-fixed smears. We reviewed the cytology slides on the basis of representative cytologic FN findings such as abundance of follicular epithelial cells, presence of micro-follicular structures, abundant cell crowding, abundant dispersed isolated cells, homogenous nuclear morphology, lack of nuclear grooves, lack of colloid material and lack of macrophages with reference to previous reports and the Bethesda system for reporting thyroid cytology.<sup>1,2,10</sup> Regarding HCN, we looked only for the characteristic findings of Hurthle cells such as abundant finely granular cytoplasm, enlarged, central or eccentrically located,

round nucleus, prominent nucleolus, small cells with high nuclear/cytoplasmic ratio (small cell dysplasia), and large cells with at least 2× variability in nuclear size (large-cell dysplasia). However, for the cytologic review we applied the same cytologic standards as in FN. After slide review, cytologic diagnosis was compared with the histologic diagnosis of each case. We selected the cases which satisfied the standard adequacy criteria for interpreting thyroid cytology. The standard adequacy criteria is the presence of at least 6 groups of follicular cells in total on stained smears, with a minimum of 10 cells in each group.<sup>11</sup>

## Results

The patients ranged in age from 16-85 yr. A majority of the cases were female and only 4 cases were male. Ultrasonographic findings showed that 8 cases were benign, 6 cases were suspicious for malignancy, and 40 cases were indeterminate. Among the 54 cases in which surgery was performed, 48 (88.9%) were diagnosed as FN and 6 (11.1%) were diagnosed as HCN in the preoperative FNAC. Of the 54 cases, 32 (59.3%) were diagnosed as FA, 4 (7.4%) were Hurthle cell adenoma (HCA), 2 (3.7%) were FC. A total of 38 cases (70.4%) were consistent with FN and the other cases included 10 (18.5%) nodular goitres, 2 (3.7%) PCs, and 2 (3.7%) Hashimoto's thyroiditis. All 6 cases which were cytologically diagnosed as HCN were proven histologically to be non-FN. Thus, the FNAC diagnostic accuracy for FN was 70.4% (Table 1). Regarding the clinic-pathologic characteristics of the 38 cases which were diagnosed as FN. The age varied from 17 to 62 years and the average age was 38.4 years. The tumor sizes evaluated from the lobectomy or total thyroidectomy specimens ranged from 0.4 cm to 4.5 cm with an average size of 2.29 cm. The lesion sites included the right lobe, left lobe, and isthmus. Histologic subtypes were as follows: microfollicular, norm follicular, oncolytic, microfollicular with trabecular, and micro-follicular with papillary hyperplasia. These cases had generally sufficient cellularity for a proper diagnosis, and the majority showed the characteristic cytologic findings including abundance of follicular epithelial cells, presence of microfollicular structures, abundant cell crowding, abundant dispersed isolated cells, homogenous nuclear morphology, lack of nuclear grooves, lack of colloid material and lack of macrophages. Among these cytologic features, high cellularity, abundant micro follicles, abundant cell crowding, and homogenous nuclear morphology were especially important features for the FN cytologic diagnosis (Table 2).

Table 1  
Cytohistological correlation of follicular neoplasm of thyroid

Cytological diagnosis	No. of cases (%)	HC Corresponds to FN (%)				HC Corresponds to NFN (%)			
		FA	HA	FC	Total	NH	PC	HT	Total
FN	48(88.9)	32(59.3)	4(7.4)	2(3.7)	38(70.4)	8(14.8)	2(3.7)	-	10(18.5)
HCN	6(11.1)	-	-	-	-	2(3.7)	2(3.7)	2(3.7)	6(11.1)
Total	54(100)	32(59.3)	4(7.4)	2(3.7)	38(70.4)	10(18.5)	4(7.4)	2(3.7)	16(29.6)

HD, histologic diagnosis; FN, follicular neoplasm; HCN, Hurthle cell neoplasm; NFN, non-follicular neoplasm; FA, follicular adenoma; HA, Hurthle cell adenoma FA, oncocytic variant; FC, follicular carcinoma; NH, nodular hyperplasia; PC, papillary carcinoma; HT, Hashimoto's thyroiditis

Table 2  
Cytologic features of thyroid follicular adenoma in FNAC

Cytologic features	HD Corresponds to FN (%)				HD Corresponds to NFN (%)			
	FA (n=32)	HA (n=4)	FC (n=2)	Total (n=38)	NH (n=8)	PC (n=2)	HT (n=0)	Total (n=10)
High cellularity	32(100)	4(100)	2(100)	38(100)	8(100)	2(100)	0	10(100)
Abundant microfollicles	32(100)	4(100)	2(100)	38(100)	8(100)	2(100)	0	10(100)
Abundant cell crowding	32(100)	4(100)	2(100)	38(100)	8(100)	2(100)	0	10(100)
Abundant dispersed isolated cells	30(93.8)	2(50)	2(100)	34(89.5)	6(75)	0	0	6(60)
Homogenous nuclear morphology	32(100)	4(100)	2(100)	34(100)	6(75)	0	0	6(60)
Lack of nuclear grooves	32(100)	4(100)	2(100)	38(100)	8(100)	2(100)	0	10(100)
Lack of colloid material	30(93.8)	2(50)	2(100)	34(89.5)	8(100)	2(100)	0	10(100)
Lack of macrophages	30(93.8)	2(50)	2(100)	34(89.5)	8(100)	2(100)	0	10(100)

FNAC, fine needle aspiration cytology; HD, histologic diagnosis; FN, follicular neoplasm; NFN, non-follicular neoplasm; FA, follicular adenoma; HA, Hurthle cell adenoma

FA, oncocytic variant; FC, follicular carcinoma; NH, nodular hyperplasia; PC, papillary carcinoma; HT, Hashimoto's thyroiditis.

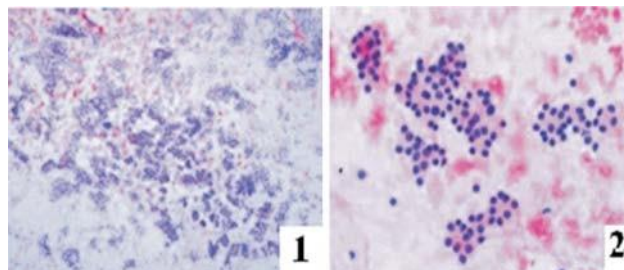


Fig. 1. Follicular adenoma (FA) shows low power view of fine needle aspiration cytology (FNAC) shows high cellularity composed of abundant micro follicles. Fig (2) The crowded follicular cells have homogenous nuclear morphology composed of round nuclei, evenly dispersed, granular chromatin and faint nucleoli

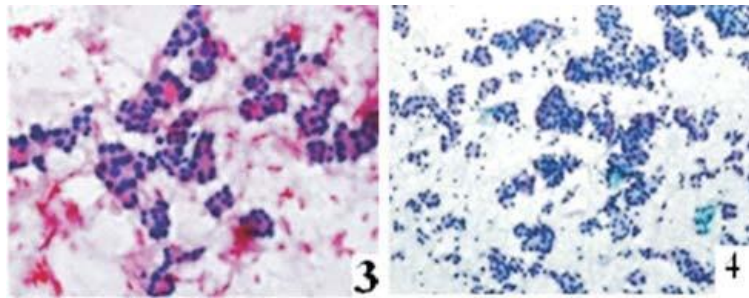


Fig. 3. Microfollicles contain small amounts of colloid. Fig.(4) Hurthle cell type. The aspirate is very cellular and consists almost exclusively of Hurthle cells in small crowded arrangements

### Discussion

The purpose of cytological or pathological examination reports is to provide clinicians appropriate guidelines for the treatment of patients, including surgery to the clinicians.<sup>12</sup> In the field of cytology, several report formats have been developed for this purpose, and presently, most reports are provided using categorical terms. Several forms of categorical diagnosis have been introduced. Generally, they include categories of unsatisfactory, benign, suspicious for malignancy, malignancy, and some forms have additional categories such as indeterminate, atypical, or follicular neoplasia.<sup>13</sup> FA is defined as solitary encapsulated nodules arising in an otherwise normal thyroid that lack evidence of capsular or vascular invasion.<sup>9</sup> HCN is considered a biologically different disease entity from FN, but is reported in the same category as FN with the additional mention of the possibility of HCN. Traditionally, FN and HCN were ambiguously classified in cytology because of the limitations of their cytologic diagnosis. Recently, the Bethesda system for reporting thyroid cytopathology was introduced which classified FN/HCN in the independent category.

The traditional category of atypia includes the cytologic findings of suspicious FN/HCN in the terminology of follicular lesion of undetermined significance.<sup>10</sup> However, the cytologic diagnosis of FN/HCN remains clinically controversial when compared to PC, which provides effective guidelines for the clinician.<sup>14,15</sup> Using FNAC, the diagnostic accuracy of PC is more than 90%, but the distinction between malignancy and benign in FN or HCN is impossible because surgery is mandatory for the definitive diagnosis of FC or Hurthle cell carcinoma.<sup>16</sup> In this guideline, FNAC is recommended for nodules of more than 1.0 cm in size, nodules less than 1.0 cm in size but associated with risk factors, cystic nodules more than 2.0 cm in size, or patients with Hashimoto's thyroiditis because it is more commonly associated with PC.<sup>17</sup> The revised edition also used the Bethesda system for the provision of treatment guidelines.

For unsatisfactory cases, a repeat examination with follow-up or consideration of surgery is recommended. For benign cases, additional examination or treatments are not necessary. In the atypia category, because the malignancy rate is approximately 5-15%, a repeat FNAC with consideration of surgery is necessary. The category of suspicious malignancy or malignancy is indication for lobectomy or total thyroidectomy. For the FN, when the autonomous nodules are not found in

the thyroid scan, lobectomy or total thyroidectomy is recommended. For the HCN, lobectomy or total thyroidectomy is recommended without a thyroidscan.<sup>1</sup> In the FN or HCN cases, although a few cytologic findings can be helpful for the suspicion of FN/HCN, the prediction value of malignancy is relatively low.<sup>18</sup> FNAC cannot provide definitive criteria for the distinction between benign and malignancy when FN/HCN is suspected.

In these studies, the cytologic diagnosis rate of FN was approximately 10% and a majority of FA or FC cases confirmed by histologic diagnosis showed a previous cytological diagnosis as benign, nodular hyperplasia, and even as PC.<sup>19,20</sup> Most pathologists do not have sufficient experience with FN/HCN. In FNAC, the most important causes of diagnostic misinterpretation were overlapping cytological features among follicular-derived lesions and inadequate/suboptimal specimens. Especially, the follicular variants of PC, FN, and adenomatous hyperplasia show overlapping cytological features making the diagnosis of FN/HCN more difficult.<sup>19,22</sup>

Although difficult, the ultimate purpose of FNAC in FN/HCN cases is to isolate FC. The present study showed the diagnostic specificity of FA including HCA was 64%, with a malignancy rate of 11% when a histologic correlation was conducted. Among the malignancies, 2 FC and 4 PCs were identified. The malignancy rate in the present study did not reach the same level as with the Bethesda system, but PCs were not exclusively included. Therefore, PC was successfully screened by FNAC with the relevant cytological diagnosis, and the diagnostic specificity of FN by FNAC was relatively high when compared with the histologic diagnosis. Specifically, among the FNs, 2 FC was successfully identified even though the number of cases was small. These results are well correlated with the clinical experience that lobectomy or total thyroidectomy is recommended for the cytologically suspected FN. Because this category predicts the existence of FC to some extent and leads to surgical treatment, this category has sufficient value in FNAC.

The present study started with the selection of cytologically diagnosed FN, and cases were chosen where correlation with histologic diagnosis was available. Therefore, this was a slightly different approach when compared with pre-existing methods which started with the histologically confirmed FA or FC cases and followed by analysis of their previous cytological diagnoses. However, this approach generally results in a low diagnostic FNAC rate in the case of FNs.

## **Conclusion**

This study shows that FNAC for thyroid FN is a useful primary screening method because when FN is diagnosed by FNAC, the rate of FN histological diagnosis is relatively high, and however, adequate sampling and experience is a prerequisite for this procedure.

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**Conflict of Interest:** None

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