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Cytological Diagnosis of Follicular Patterned Lesion of Thyroid Nodule and its Follow-up Histopathology

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Abstract

The follicular patterned lesion of thyroid nodules is an exciting topic because it is not clear whether the lesion is benign or malignant. It comprises hyperplastic/adenomatoid nodules, follicular adenoma, follicular carcinoma and follicular variant of papillary carcinoma. The cytological diagnosis of atypia of undetermined significance/Follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm and suspicious for malignancy remains controversial in terms of management. The study aimed to examine the extent of invasion of malignant lesions in follow-up histopathology diagnosed as undetermined lesions cytologically. A total of 256 cases were included in this study; among these, 199 cases were benign lesions, 15 cases were non-diagnostic and 42 cases were diagnosed either of uncertainty for malignancy with cellular atypia or malignancy. Subsequent follow-up resection and histopathology were done with 48 cases (18.75%), which comprises 1 non-diagnostic, 10 benign lesions, 21 atypia of undetermined significance/Follicular lesion of undetermined significance, 7 Follicular neoplasm/Suspicious for a follicular neoplasm, 5 suspicious for malignancy and 4 malignancies. Also, 6 Follicular variant of papillary thyroid carcinoma, 6 classic papillary carcinoma, 5 follicular carcinoma and 1 anaplastic carcinoma were diagnosed in follow-up resection histopathology of 48 cases. Thirty eight cases were of undetermined significance of malignancy with cytological features of the follicular lesion. Four Follicular variant of papillary thyroid carcinoma, 2 follicular carcinoma and 1 papillary carcinoma were diagnosed in 21 resected cases cytologically reported as Atypia of undetermined significance/Follicular lesion of undetermined significance with malignancy risk of 33.33%. Three malignancies in follicular neoplasm/suspicious for a follicular neoplasm with a risk of 42.85% and 4 malignancies in suspicious malignancy group with a risk of 80% were found. The average risk of malignancy of these three undetermined categories was reduced to 24.24% from 42.42% upon reclassification of the Follicular variant of papillary thyroid carcinoma. All the Follicular variants of papillary thyroid carcinoma diagnosed by histopathology were non-invasive regarding lymph node involvement and microvascular or capsular invasion.

Keywords: Follicular patterned Lesion, Thyroid nodule, Cytology, Follow-up histopathology.

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Introduction

Follicular patterned lesions of thyroid nodules are the most common surgical specimen reviewed in the laboratory by surgical pathologists.[1] To address the variability of cytological findings in the fine needle aspiration cytology (FNAC) reports, the Bethesda system for reporting thyroid cytology was recommended in 2007 which includes six diagnostic categories: I=non-diagnostic, II=Benign, III=atypia of undetermined significance/follicular lesion of undetermined significance, IV=follicular neoplasm/suspicious for a follicular neoplasm, V=suspicious for malignancy, and VI=malignant.[2] Atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm /suspicious for follicular neoplasm and suspicious for malignancy categories are reported cytologically with the uncertainty of malignancy. There is a tendency of increasing the diagnosis of atypia of undetermined significance/follicular lesion of undetermined significance by the pathologists and follow-up histopathology revealed more malignancies like follicular variant of papillary carcinoma and a significant portion of these tumours are non-invasive.[3-5] Most authors agree that cytological features cannot reliably distinguish conventional papillary thyroid carcinoma from non-invasive neoplasm and complete excision and evaluation of the capsule is required for diagnosis.[6] Follicular neoplasm/suspicious for follicular neoplasm and suspicious for malignancy categories have the risk of malignancy ranging from 20% to 30% and 60% to 75% respectively and 61.2% to 86.0% of them potentially referring to surgery in practice.[8] Some investigators have proposed to diagnose a proportion of these follicular lesions of undetermined significance as non-invasive neoplasm rather than carcinoma.[10,11] The cytological diagnosis of atypia of undetermined significance/follicular lesion of undetermined significance leads both the clinician and the patient to become anxious for its uncertainty because of the repetition of the procedure. Moreover, the wide variation of malignant potentiality leads us to a perplexing situation.[12] We have been encouraged to explore the nature of invasion of cytologically diagnosed follicular patterned lesions of thyroid nodules in follow-up histopathological examination for assessment of their compatibility with recently proposed diagnosis of non-invasive follicular thyroid neoplasm which can help in appropriate clinical management.

Materials and methods

A total of 256 patients having thyroid nodules attending Khulna City Medical College Hospital and Khulna Medical College Hospital during the period from July 2020 to June 2022 were included in this prospective cross-sectional study. After approval of the protocol by the ethical committee of the institution, informed consent was taken from each participant considering the inclusion and exclusion criteria. All aspirates were performed aseptically with 2 to 12 passes of needles of the combination of 25, 23, and 21- gauge for subsequent laboratory procedures and cytological examination under the microscope. Direct smears were made in all cases and all were alcohol fixed and stained with Papanicolaou or H&E. Cell blocks were also made if the aspirated material was sufficient. All smears should contain at least 6 groups of epithelial cells with 10 cells per group to be adequate for cytological evaluation.[13] All the fine needle aspirates were diagnosed according to The Bethesda System for Reporting Thyroid Cytology (TBSRTC). Repeat fine needle aspiration cytology is recommended for the cytological diagnosis of atypia of undetermined significance/-follicular lesion of undetermined significance (AUS/FLUS) leading both the clinician and the patient to become anxious. On the other hand, clinical management of cytological diagnosis of follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) and suspicious for malignancy are lobectomy and total thyroidectomy respectively.

During microscopic examination, a considerable proportion of smears having hyper-cellular contents with scant colloid were seen and these were unlikely to be benign thyroid lesions but the cells showed nuclear enlargement and focal overlapping resembling follicular neoplasm. The available cell block preparation did not show micro

follicles sufficient for the diagnosis of a follicular neoplasm. There were no obvious features of papillary carcinoma such as nuclear groove, pseudo inclusion, or papillae in these specimens. These cases were cytologically categorized as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS).

Specimens considered to be suspicious for a follicular neoplasm were hyper-cellular and predominantly arranged in micro-follicles. Colloid was scanty and very often cells were crowded and overlapped showing marked variation of nuclear size and outline and having hyper-chromatic nuclei. These groups were designated as follicular neoplasm/suspicious for follicular neoplasm (FN/SFN).

Specimens diagnosed as suspicious for malignancy (SM) had cells with the features for diagnosis of AUS/FLUS and FN/SFN as well as intra-nuclear inclusions but smears were hypo-cellular, poorly preserved, or complicated by other features such as Hurthle cell change that fall short to a definitive diagnosis of papillary carcinoma or follicular carcinoma. These are not included in the group of cytological diagnosis of follicular patterned lesions but practically the smears have cytological features of a follicular lesion and their indeterminate characters lead us to include them in an undetermined category in this study.

Pathologists have to come across lesions that cannot be categorized as 'definitely benign or malignant' in cytological diagnosis. Such lesions represent a 'grey zone' and are usually termed tumours of uncertain or borderline malignant potential and these were proposed to be designated as diagnoses of follicular tumours of uncertain malignant potential.[14] No molecular study has been able to distinguish between adenomatoid nodule, follicular adenoma, and carcinoma with 100% sensitivity and specificity. Most of the follicular lesions are either benign or malignant and these are diagnosed by follow-up histopathology, and these follicular lesions remain with uncertain risk of malignancy.[15] These three undetermined groups in TBSRTC were evaluated to determine their malignant potentialities in subsequent resection histopathology and accordingly microvascular invasion, capsular invasion and lymph node involvement were examined for all the malignant cases.

The diagnoses from the cytological examination were reviewed and if there was any discrepancy in diagnosis, the slides were reviewed by experienced pathologists and then follow-up histopathology was pursued. All the data and observations were recorded and presented in tables and charts and analysed by using a computer generated software "SPSS" 'Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA)'.

Ethical Clearance: The research protocol of this study and the informed consent form were reviewed and approved by the ethical committee of Khulna City Medical College. The written informed consent was then obtained from each participant and a unique identification number was assigned and all records were kept in a secured room to ensure confidentiality.

Results

A total of 256 cases with thyroid nodules were included in this study. Among the cases, 176 (68.75%) cases were female and 80 (31.25%) cases were male patients and ages ranging from 14 to 85 years with a median of 55 years. Follow-up resection and subsequent histopathology were done with 48 cases (18.75%). The overall results are summarized in table 01.

Table 01: Distribution of the patients in different categories (TBSRTC) with follow-up histopathology, (n=256).

TBSRTC	Category	FNAC diagnosis	Recommended management	Histopathology diagnosis
I	Non-diagnostic or Unsatisfactory	15	Repeat FNA with U/S	Resected (1) Nodular goitre
II	Benign	199	Follow up clinically	Resected (10) Nodular goitre
III	Atypia of undetermined Significance (AUS) or Follicular lesion of Undetermined Significance (FLUS)	26	Repeat FNA	Resected (21) Adenomatoid goitre=10 Adenoma=4 FVPTC=4 Follicular Ca=2 Papillary Ca=1
IV	Follicular Neoplasm(FN) or Suspicious for a follicular Neoplasm (SFN)	07	Lobectomy	Resected (7) Adenoma=4 Follicular Ca= 2 FVPTC=1
V	Suspicious for Malignancy (SM)	05	Lobectomy or total Thyroidectomy	Resected (5) Adenoma=1 Papillary Ca= 2 Follicular Ca=1 FVPTC=1
VI	Malignant	04	Total thyroidectomy	Resected (4) Papillary Ca=3 Anaplastic=1
Total	I, II, III, IV, V, & VI categories	256		48 (18.75%)

Among the 256 cases, 199 cases were benign lesions and 15 cases were non-diagnostic, 38 cases were diagnosed in indeterminate categories of AUS/FLUS, FN/SFN or suspicious for malignancy and 4 cases were malignant. Subsequent follow-up resection and histopathology were done with 48 cases (18.75%), which comprises 1 non-diagnostic (nodular goitre), 10 benign lesions(nodular goitre), 21 AUS/FLUS lesions(Adenomatoid goitre-10, Adenoma-4, FVPTC-4, Follicular Ca-2, Papillary Ca-1), 7 FN/SFN lesions(Adenoma-4, Follicular Ca-2, FVPTC-1), 5 suspicious for malignancy (Adenoma-1, Papillary Ca-2, Follicular Ca-1, FVPTC-1) and 4 malignancy (Papillary Ca-3, Anaplastic Ca-1); (Table 01).

Table 02: Cytological diagnoses of follicular lesions and pattern of invasion in histopathology with risk of malignancy, (n=33).

Diagnosis by FNA	No. of cases	Follow up Histology diagnosis	Pattern of invasion			Risk of Malignancy	Risk of Malignancy on Re classification
			Microvascular invasion	Capsular invasion	Lymph Node involvement		
Atypia of Undetermined Significance (AUS)/ Follicular lesion of Undetermined Significance (FLUS)	21	Adenomatoid goitre-10 Adenoma-4 FVPTC-4 Follicular ca-2 Papillary ca-1	0 0 1 0	0 0 1 1	0 0 0 0	33.33%	14.28%
Follicular Neoplasm (FN)/Suspicious for Follicular neoplasm (SFN)	7	Adenoma-4 Follicular ca-2 FVPTC-1	0 0	1 0	1 0	42.85%	28.57%
Suspicious for Malignancy (SM)	5	Adenoma-1 Papillary ca-2 Follicular ca-1 FVPTC-1	2 1 0	1 1 0	1 1 0	80%	60%
Total	33	33	4	5	3	42.42%	24.24%

Among the 48 resected thyroid samples, 33 cases were cytologically indeterminate categories with variable risks of malignancy. Of which, subsequent histopathology revealed 14 (42.42%) malignant tumours comprising 6 FVPTC, 5 follicular carcinomas and 3 papillary carcinomas (Table 02). In follow-up histopathology, AUS/FLUS group showed a 33.33% risk of malignancy, FN/SFN group showed a 42.85 % risk of malignancy and the suspicious malignancy group showed an 80% risk of malignancy. The microvascular invasion was seen in 4 malignant cases, capsular invasion was in 5 tumours and lymph node involvement was in 3 malignant tumours. All the cases diagnosed as FVPTC showed no invasion in their capsules partially or entirely.

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Discussion

The aim of the study was straightforward forward to explore the nature and extent of invasion of malignant follicular lesions reported cytologically as follicular patterned lesions having cellular atypia of undetermined significance. In the present study, 38 cases had follicular features in the cytology smears and these were reported as indeterminate categories of follicular lesions with varying risk of malignancy. Subsequent histopathology of 33 cases of this indeterminate category revealed 14 malignant tumours in FNAC cases with a risk of malignancy of 42.42% (Table 02). The overall risk for malignancy of 48 resected cases of cytological diagnosis in the present study was 37.5 %.

The Bethesda System for Reporting Thyroid Cytology (TBSRTC) has been proven to be an effective and robust thyroid FNA classification scheme to guide the clinical treatment of patients with thyroid nodule and recommended as a standard practice in reporting thyroid aspiration cytology by the American Thyroid Association guidelines.[7] Following this, the observation of the present study was that the average risk of malignancy in diagnosis of undetermined categories would have been reduced from 42.42% to 24.24 % in follow-up histopathology if we had not designated FVPTC as carcinoma.

In the clinical management of AUS/FLUS cytology report according to TBSRTC, repeat FNA is recommended. Incidentally, the majority of the follicular variant of papillary carcinoma (FVPTC) were diagnosed as FLUS/AUS by cytology found in the present study, and subsequent histopathology revealed 4 FVPTC which were non-invasive, 2 follicular carcinoma which had capsular invasion and one papillary carcinoma with capsular invasion. The risk of malignancy was 33.33% in this group, other indeterminate groups showed 3 malignant tumours in FN/SFN group with a malignancy risk of 42.85% and 4 malignant tumours in the SM group with a risk of malignancy of 80%. This risk of malignancy rate can be reduced to 14.28% from 33.33% in AUS/FLUS group, 28.57% from 42.85% in FN/SFN group and 60% from 80% in the SM group on reclassifying the tumour FVPTC as NIFTP (Table 02). A similar study revealed that the risk of malignancy was reduced to 5.2% from 13.6% in AUS/FLUS group, 9.9% from 15.1% in FN/SFN group and 17.6% from 23.4% in suspicious for malignancy group by the reclassification of the FVPTC as an intermediate group of the tumour.[8]

A working group of international experts including 24 thyroid pathologists critically examined a cohort of 109 patients with non-invasive encapsulated FVPTC with at least 10 years follow-up without post-operative radioactive iodine treatment, and observed that none of them developed recurrence. Following this observation, they reached a consensus in a change of nomenclature from non-invasive encapsulated FVPTC to NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) to avoid the term 'carcinoma'. The criteria for making this diagnosis included the following: 1) encapsulation or clear demarcation, 2) follicular growth pattern with less than 1% papillae, no psammoma body, and no more than 30% solid/trabecular/insular growth pattern, 3) nuclear score 2 to 3, 4) no vascular or capsular invasion, 5) no tumour necrosis, and 6) no high mitotic activity (defined as at least 3 mitoses per 10 high-power fields).[9] Moreover, in a recent study, it was acknowledged that NIFTP more often falls within a nuclear score of 2/3, and making tumours that show a nuclear score of more than 3 is highly suspicious for being a papillary thyroid carcinoma.[10]

In the present study, we considered the histologic diagnosis of FVPTC which was proposed to be designated as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[14] Nuclear pseudo inclusion and papillae are diagnostic for papillary carcinoma, and other nuclear features such as pale chromatin, nuclear groove, and crowded nuclei are more commonly seen in the AUS/FLUS category and more prominence of these findings increase the suspicion

of malignancy.[16] Cytological diagnosis of follicular patterned lesions of the thyroid including hyperplastic/adenomatoid nodule, follicular adenoma, follicular carcinoma and follicular variant of papillary carcinoma poses a great controversy whether it is benign or malignant and whether it is determined by histopathology based on encapsulation, nature of invasion and nuclear features.[17] The most undetermined group (AUS/FLUS) has a malignancy risk of 33.33% in the present study which is comparable with observations of risk of malignancy varying from 5% to 48% in AUS/-FLUS group in studies by Yang J et al and Theoharis CG et al.[12,18] We observed the decrease of malignancy risks on reclassification of FVPTC as NIFTP in present study such as 19.05% in AUS/-FLUS group, 14.28% in FN/SFN group and 20% in SM group. Similar findings were observed in a study including 3250 resected thyroid nodules with previously matched FNAC diagnoses from 3 institutions upon reclassifying the FVPTC as NIFTP, the impact on the risk of malignancy was observed and noted a reduction from 15% to 5.2% in AUS/FLUS category, from 11.2% to 3.9% in FN/SFN category and from 26.8% to 0% in suspicious for malignancy category with decrease in malignancy risk of 9.8% in AUS/FLUS group, 7.3% in FN/SFN group and 26.8% in SM group.[19] Howitt and co-workers analysed a series of 72 NIFTPs and observed the most significant decrease in the risk of malignancy of 48.6% in the SM category,[20] and similar findings have been reported by Ustun et al.[21]

The follicular variant of papillary thyroid carcinoma is the second most common variant of carcinomas of the thyroid after the classic variety. This tumour clinically presents either as a single nodule or arises against a background of multi-nodular goitre having partial or complete capsule or without capsule. Straight forward diagnosis of FVPTC is not too much difficult in cytology but some cases show multifocal rather than diffuse distribution of nuclear features of papillary carcinoma leading to a controversial diagnosis. Some authors have suggested that these cases should be termed as well-differentiated tumours of uncertain malignant potential corresponding to minimally invasive tumours of one of the three varieties in WHO classification to prevent overtreatment surgically. The current World Health Organization (WHO) classification of thyroid neoplasms acknowledges the existence of 3 variants of follicular thyroid carcinoma: minimally invasive, widely invasive, and encapsulated angioinvasive.[13,22,23]

The diagnosis of FVPTC is a histopathological variety and it is not a cytological diagnosis and is mostly found following AUS/FLUS reporting in the present study. What are the factors influencing the diagnosis of this group of indeterminate cytology? The most important factor is reactive change mimicking atypia associated with cystic degeneration, thyroiditis, physical or chemical trauma, radiation, and other non-specific causes.[24] Secondly, perifollicular fibrosis, in which there is basement membrane-like material outlining the follicles occurs in sporadic colloid nodules, adenomatoid hyperplasia, and in paediatric thyroid cancer following radiation and also in thyroid lesions in elderly patients.[25,26] Thirdly, benign cellular components mimicking AUS/FLUS, as the parathyroid gland is occasionally aspirated during thyroid FNA and leading to a diagnosis of AUS/-FLUS.[27]

The observations of the present study were concordant with many literature reviews and proposals of pathologists for some changes of criteria in the histopathologic diagnosis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features which might influence the approach to cytological reporting and clinical management.[28] Two recent studies demonstrated independently with this issue, one including 52 cases with a median follow-up of 6.3 years and the other reported 8 cases with a mean follow-up of 12 years, all of which showed a negligible risk of nodal metastasis, distant metastasis and recurrence.[29,30] In an international collaborative study involving four tertiary hospitals including 79 patients with NIFTP of at least 4 cm. in size, all patients were disease free with a median

follow-up of 6.7 years, and another group including 37 individuals that did not receive radioactive iodine therapy and based on these results, it was evident that large NIFTP can be safely and adequately managed by surgical treatment alone as long as the tumour capsule is entirely sampled to exclude invasion.[31]

Some cohort studies such as one by Parente et al.[32] from Canada and another one by Kim et al.[33] from Korea have found up to a 6% rate of predominantly nodal metastasis in NIFTP patients with the tumours having less than 1% papillae and without papillae, the metastatic risk was up to 2-5%. In these studies, the molecular profiles were not estimated, so confidently one can 'not include these as invasive carcinomas.

The major pitfalls of the present study are most importantly molecular diagnostic tests were not performed in the laboratory procedures for the study subjects; secondly, a core needle biopsy was not performed before resection; thirdly, inter-observer variation during the cytological examination of the smears was not calculated statistically; fourthly, a long term cohort of FVPTC cases is required to evaluate the prognosis in the follow-up study and finally, the relationship between the extent of nuclear features and invasiveness of tumours was not determined and till now there is a long way to go ahead.

Conclusion

Follicular patterned lesions of thyroid nodules diagnosed by fine needle aspiration cytology have variable risk of malignancy and Follicular variants of papillary carcinoma cases diagnosed in follow-up histopathology are mostly non-invasive considering lymph node involvement and capsular or microvascular invasion.

What does this study add to existing knowledge: Most of the cases of FVPTC were diagnosed with great uncertainty as AUS/FLUS by cytological examination and exclusion of this diagnosis as carcinoma reduces the rate of malignancy in the cytological diagnosis of the follicular patterned lesion in subsequent histopathology.

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