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Usefulness of Core Needle Biopsy in Diagnosis of Thyroid Nodule Comparing with Fine Needle Aspiration Cytology

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Abstract
Background: *Fine needle aspiration (FNA) is a reliable test for diagnosis of thyroid nodule. Sometimes, repeated aspiration does not yield diagnostic material. Core needle biopsy (CNB) has been introduced as an alternative for preoperative assessment of thyroid nodule.*
Objective: *To compare the adequacy and accuracy of FNA to that of Core needle biopsy in same patient using histologic diagnosis as gold standard by follow-up resection.*
Methods: *We compared the adequacy and accuracy of Fine needle aspiration (FNA) with core needle biopsy (CNB) in a total of 189 patients who underwent both tests.25 cases of a total 32 atypical, suspicious and positive cases had follow-up resection for comparison. Accuracy were calculated by using histologic diagnoses.*
Results: *The adequacy rate for core needle biopsy (84.1%) was significantly higher than that of FNA (69.31%; P <0.001)), but the combined adequacy was significantly higher than that for either test alone (88.88%; P<0.001). Overall concordance between the tests was 69.8%. In 37 cases, the core was adequate and negative (33 cases) or atypical (4 cases) and the aspirate was non-diagnostic; in 9 cases, the aspirate was adequate and negative (5 cases) or atypical (4 cases) and the core was non-diagnostic. In 5 cases, the FNA diagnosis was atypical and the core was negative; the follow-up histologic examination of 4 cases revealed 2malignancies. On review, it was observed that core biopsy missed the lesion.*
Conclusion: *Core needle biopsy has a higher adequacy and accuracy rate than FNA but seems less sensitive, especially for papillary carcinoma. The combination of FNA and core needle biopsy seems to have the highest adequacy rate and usefulness.*
Keywords:*Thyroid, Cytology, Fine-needle aspiration, Core needle biopsy, Diagnosis, Adequacy, Accuracy.*

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I. Introduction:

Fine-needle aspiration (FNA) cytology is an established reliable test for the preoperative diagnosis of thyroid nodule.[1.2] Accuracy and advantages of FNAare well known worldwide but there are some limitations of diagnosis and disadvantages.[3] In some cases, even repeated aspiration does not yield diagnostic material and aspirates of borderline adequacy may be a source of diagnostic error.[4]False-negative diagnoses may arise from inadequate sample, missing of lesions, diffusely growing malignant tumours or from error in interpretation.[5]It is clear to all who perform these tests that there are some nodules that remain difficult to obtain high-quality diagnostic material even with experienced operators.[6]Core needle biopsy (CNB) of thyroid was introduced as an alternative method to obtain tissue for preoperative diagnosis.[7] Diagnostic method by using core needle biopsy is well studied in other body sites, but few reports are available related to the yield and accuracy of core needle biopsy of the thyroid, while studies comparing FNA and core needle biopsy of many other organs are available, some of the studies compare the 2 methods on different patients and different lesions, others compare the results of core needle biopsy primarily in patients who have had previously non-diagnostic aspirates.[8.9] A study with a series of 100 patients suggests that the 2 tests are complementary and the adequacy rate is highest with both tests done together.[10] Recently some techniques have been improved in core needle devices (thinner needle and automatic devices) and high resolution ultrasound machine,[11] some experiments explored that in cases with the

presence of malignancy and parathyroid lesions, the CNB based histologic examinations yielded more confirmative diagnosis,[12] and better performances can be achieved with CNB in unsatisfactory, inadequate and paucicellular FNA in some nodules with calcification or degeneration.[13] The non-diagnostic results of previous FNA are the most widely accepted indications for core-needle biopsy.[14]

In Bangladesh, thyroid nodule is frequently found in clinical practice, diagnosis is done in collaboration with an important role of the radiologists. We have been encouraged to perform core needle biopsies of the thyroid,with the assistance of radiologist especially in patients who had a previous non-diagnostic aspiration or had a nodule that is difficult to aspirate. We sought to compare the adequacy rate and accuracy of FNA and core needle biopsy in patients who underwent both procedures.

II. Methods:

A total of 189 patients who underwent FNA and core needle biopsy of thyroid nodule from July 2016 to June 2018 at sarkari kormochari hospital, Dhaka, and Dhaka Medical College Hospital, Dhaka were included in this study.

The indications for core needle biopsy varied for the cases included in this study during this period, the cases were selected at the request of clinician when the previous aspirate was nondiagnosticand the cases were selected considering the acceptability of the both procedures by the patients. Also the patients had to be suitable for the procedure after exclusion of some clinical abnormalities particularly haemorrhagic disorders by routine haematological screening tests. During the study period, we observed that the complications were infinitesimal, so, number of cases were increased up to 60% of total attending cases in aforementioned centers.

The diagnoses from these biopsies were reviewed and compared. In cases in which there was a discrepancy in the diagnosis, the slides were reviewed by senior pathologists and later on histologic follow-up pursued.Allaspirates were performed by pathologists under ultrasound guidance with immediate evaluation. Between 2 and 12 passes were made using a combination of 25-, 23-, and 21 gauge needles for the FNA. Direct smears were made in all cases, and all were alcohol fixed and stained with Papanicolaou or H&E. If sufficient material was obtained, cell blocks were also made. At the same sitting and after the FNA, a core needle biopsy was performed using an 18-, or 20- gauge needle. This material was formalin fixed and stained with H&E.

Aspirates and core needle biopsy specimens were classified as adequate or nondiagnostic. For the purposes of this study, all negative smears and diagnostic smears had to contain at least 6 groups of follicular epithelial cells with 10 cells per group to be considered adequate.[15] Smears made from aspirates consisting of abundant colloid and fewer cells than this were classified as a colloid nodule and for the purpose of this report, were treated as negative and adequate. Criteria of adequacy for core needle biopsy have not been previously defined and for the purposes of this study, the presence of any identifiable thyroid tissue was considered adequate.

FNA samples fulfilled the criteria to be adequate, were classified as negative and atypical, "suspicious" or positive. For the purpose of reported analysis, atypical, suspicious, or positive cases were grouped together.During cytologic and histologic examinations, specimens considered suspicious for a follicular neoplasm were hypercellular and predominantly arranged in micro-follicles, colloid was scarce, and often the cells were crowded, nuclei were hyperchromatic, overlapped and showed variation of nuclear size and outlines and these are reported practically by pathologists designated as cellular follicular lesion. We prefer to categorize this group of cases as suspicious rather than positive for a follicular neoplasm as some pathologists do because it is not always possible to distinguish nodules of hyperplastic lesions from those of neoplasms, and some of clinicians may misinterpret the word positive to mean malignant. However, this change of designation does not influence on treatment of the patients because they are treated the same as if they had been given a diagnosis positive for a follicular neoplasm (i,e, they underwent surgery).

Specimens diagnosed as atypical, which contain most often only 1 or 2 groups of cells with enlarged crowded nuclei, pale chromatin, and rare grooves, and papillary carcinoma can not be ruled out. Nuclear inclusions were not typically identified.Specimens suspected for a Hurthle cell neoplasm contained a monomorphous population of Hurthle cells, which were often small, uniform, and dyscohesive, considered suspicious.

Specimens diagnosed as suspicious for papillary carcinoma had cells with the features of atypical diagnosis as well as intranuclear inclusions but were hypocellular, poorly preserved, or complicated by other features (such as Hurthle cell change) that did not allow a definitive diagnosis to be made.

Specimens containing cells having definite cytological features of malignancy such as groups cells having enlarged nuclei, papillae formation, pale nuclei, grooves and intranuclear inclusions, were considered positive.

For the purposes of this study, to analyze and evaluate the outcome of this series a total of 25 cases which underwent subsequent follow-up resection had been considered to determine accuracy and sensitivityas a "gold standard" and the non-diagnostic results were included in negative category. Because this represented only 13.2% of all cases (although 78.1% of all atypical, suspicious, and positive cases), an overall accuracy is not

reported. Although, the accuracy of the 2 techniques is compared within specific diagnostic categories as described subsequently.
Categorical analysis was done using a 2-tailed Fisher exact test.

III. Results:

All the cases included in the study were reviewed. The series involved 151 women and 38 men with ages ranging from 16 years to 81years (median, 52 years). For the all 189 patients, the aspirate and the core were performed at the same sitting. The cores were all 21-, 20- or 18 gauge cores. All consisted of a single pass. No clinically significant complication from core needle biopsy was observed.

The overall results are summarized in Table-1. Among the diagnostic categories, most of the cases were 'negative' by both tests (98/189, [51.85%]). The majority (25/32, [78.1%]) of all atypical, suspicious, and positive cases had follow-up resection for comparison and this is only 13.2% of the total series. Follow-up resection of total 25 cases revealed 13malignancies in 13 patients, including 6 papillary carcinomas, 3 follicular variant of papillary carcinoma, 1 follicular carcinoma, 1 medullary carcinoma, 1 anaplastic carcinoma, 1 lymphoma.

Table-1: Distribution of patients with thyroid nodules in different categories diagnosed by FNA, Core biopsy and follow-up resection histology; (n=189).

No. of cases in different diagnostic categories	Diagnoses by FNAC	Diagnoses by subsequent CNB	No. of cases with follow-up resection	No. of cases diagnosed malignant
21	Nondiagnostic	Nondagnostic	0(0%)	0
33	Nondiagnostic	Negative	1(3%)	0
4	Nondiagnostic	Atypical, suspicious or positive	2(50%)	2
5	Negative	Nondiagnostic	0(0%)	0
98	Negative	Negative	4(4%)	0
2	Negative	Atypical, suspicious or positive	1(50%)	1
4	Atypical, suspicious or positive	Nondiagnostic	2(50%)	1
5	Atypical, suspicious or positive	Negative	4(80%)	2
17	Atypical, suspicious or positive	Atypical, suspicious or positive	11(64.7%)	7
Total 189	189	189	25(13.2%)	13

The adequacy rate for core needle biopsy (84.1%) was significantly higher than that of FNA (69.31%; P<0.001), but the combined adequacy was significantly higher than that for either test alone (88.88%; P<0.001). Overall concordance between the 2 tests was 71.95%. Discordant results were observed in 53 cases (28.04%), in 37 cases, the core was adequate and negative (33 cases) or atypical (4 cases) whereas aspirate was nondiagnostic; in 9 cases the aspirate was adequate and negative (5 cases) or atypical (4 cases) whereas core was nondiagnostic (Table-1).

There were 4 cases in which the FNA specimen was atypical, suspicious, or positive and the core specimen was nondiagnostic. Resection in 2 cases revealed 1 follicular variant of papillary carcinoma, and 1 follicular adenoma. There were 5 cases in which the FNA was atypical and the core was negative; follow-up resection of 4 cases revealed malignancy in 2 cases by histologic examination which support the FNA diagnosis in 2 cases. These 2 malignant cases were papillary carcinoma. Here, it seemed that the core biopsy missed the lesion.

There were 2 cases in which the core needle biopsy specimen was atypical and the FNA specimen was negative; resection in 1 case supported the core biopsy diagnosis and showed a papillary carcinoma. In the second case, a resection only showed hyperplasia with microfollicular areas that were present in the core needle biopsy specimen. There were 4 cases in which the core needle biopsy diagnosis was atypical, suspicious, or positive and the FNA diagnosis was nondiagnostic, the resection in 2 cases with follow-up showed 1 follicular variant of papillary carcinoma and 1 follicular carcinoma. The follicular carcinoma had a microfollicular architecture in the resection and core needle biopsy specimen, here the fine-needle aspiration missed the lesion.

In the entire series, there were no cases in which both the aspirate and core biopsy specimen yielded a false-negative result, although only 4 patients with negative results in both the procedures underwent resection and confirmed by histologic examination. However there were false-negative diagnosis on aspirate butcore needle biopsy specimens detailed subsequently as 4 cases were nondiagnostic and 2 cases were negative by aspiration but CNB results were positive. In this series, 58 cases were non-diagnostic by FNA results (30.68%), whereas 30 cases were non-diagnostic in subsequent CNB (15.9%, [Table-1]).

Table-2: Showing diagnoses by FNA and Core biopsy confirmed by follow-up histologic examination. (N=25)

True positive cases diagnosed by FNA	True positive cases diagnosed by CNB	True negative cases diagnosed by FNA	True negative cases diagnosed by CNB	False positive cases diagnosed by FNA	False positive cases diagnosed by CNB	False negative cases diagnosed by FNA	False negative cases diagnosed by CNB
10	10	5	8	7	4	3	3

Among the total 189 cases, 32 cases (16.9%) were diagnosed atypical, suspicious, or positive by both the test procedures, and 25 cases had follow-up resection for histologic diagnosis (Table-2). In 15 cases, diagnoses of FNA were supported by follow-up resection and in 10 cases FNA diagnoses were discordant with resection histology. On the other hand, in 18 cases, diagnoses of CNB were supportedby follow-up resection and in 7 cases, CNB diagnoses were discordant with resection histology.

Table-3:Showing accuracy, sensitivity and predictive values of core-needle biopsy and FNAC, (N=25).

Accuracy of FNAC	Accuracy of Core- needle biopsy	Sensitivity of FNAC	Sensitivity of Core needle biopsy	+ve predictive value of FNAC	+ve predictive value of core needle biopsy	-ve predictive value of FNAC	-ve predictive value of core needle biopsy
60%	72%	76.92%	71.1%	58.82%	71.42%	62.5%	72.7%

Accuracy of core biopsy (72%) is higher than accuracy of fine-needle aspiration (60%),[Table-3]. Sensitivity of FNA (76.92%) is much higher than core biopsy (71.1%) [Table-3]. Interestingly, negative and positive predictive values of core biopsy is slightly higher than that of FNA procedure.

IV. Discussion:

The aim of this study was to compare the yield and accuracy of FNA with that of core needle biopsy of thyroid nodule using histologic examination as a "gold standard". Overall, our results with core needle biopsy are similar to those reported by others. In the present study, the adequacy rate for core needle biopsy was higher than that for FNA, but the adequacy rate for the combination of tests was highest. This supports the conclusion of other authors that the 2 tests are complementary.[10]

Interestingly, in the cases with follow-up, it was apparent that there were issues of accuracy with the core needle biopsy. In 5 cases, the core needle biopsy seemed to miss the lesion of interest and instead they showed benign thyroid tissue. On review, it was not possible to determine how the pathologist would be able to tell the core had hit a benign tissue or missed the true lesion. Moreover, to date, no criteria have been suggested for adequacy of core needle biopsy specimens. These results suggest that cellularity would be a poor measure of adequacy because in these cases all had plenty of material. Furthermore, here adequacy is not the only determining factor for evaluation, relative position of the biopsy needle with the lesion, location and techniques are important influencing factors on sampling of tissues during core biopsy procedure. To minimize the sampling error, multi-dimentional approach should be considered during core biopsy particularly the position of the needle and identification of the lesion by high resolution imaging instruments. Recent development of some devices and advanced techniques and instruments may lead us to raise a question of number of core to improve the performance to minimize the missing of the lesions of interest which can be explored by further study with core needle biopsy technique. This is an important issue of sampling during core biopsy which may arise regarding the operator's techniques and the applications of instruments for this purpose.[11]These have emphasized the fact that the adequacy of specimens during sampling of core biopsy can be determined by the skill of operator performing the procedure.

Although FNA is an excellent test and considered the gold standard in diagnosis of thyroid nodule, but it is increasingly apparent that the size of the lesions to be aspirated continues to decrease, which makes it difficult to obtain an adequate sample for evaluation.[16] Our results suggest that core needle biopsy is a safe and effective way to increase the yield of thyroid biopsy.

The cases included in this study represent a subset of all thyroid biopsies performed at the institutions afore mentioned, and as such they may not be representative of the results of FNA or core needle biopsy of all thyroid nodules throughout the country. However, not all thyroid nodules are suitable for core needle biopsy, and it is up to the radiologist to decide whether he or she feels comfortable aspirating a particular lesion, and different radiologists have different levels of enthusiasm for the technique. For this reason, the adequacy and accuracy of FNA reported herein may not reflect the adequacy of FNA of all thyroid lesions. In the study of present series, the adequacy rate of FNA alone (69.31%) is lower than in many previously published series.[17] In

fact, some lesions in this series underwent core biopsy not selected by systematic random sampling method rather at the request of clinician because the original aspirate was non-diagnostic. This suggests that in such cases it may be more difficult to aspirate than those reported in other series of thyroid nodules in which only aspiration was performed. Finally, in every case, the FNA was performed before the biopsy, and this might have distorted the material to some extent that could be obtained at core needle biopsy. However, the data presented in this report represent a direct comparison of the 2 techniques on the same nodule performed at the same setting in the vast majority of cases. Observations may differ from this study if FNA and core biopsy would have been done on different patients.

On the other hand, some authors have emphasized that poor specimen quality, in terms of cellularity and preservation, may be the underlying root cause of misdiagnoses in FNA of the thyroid and after an intervention emphasizing on increased supervision and training of those who perform aspiration, it was observed that accuracy had been increased significantly but at the cost of increased nondiagnostic rate.[18] This issue of sampling technique during aspiration is intimately related to the operators and not markedly to the clinicians but it is not clear that how much acceptable by the clinicians. In addition, some efforts have been tried at some institutions, but much success were not reported.[18] Also, it is clear to all who perform these tests that there are some nodules that remain difficult to obtain high-quality aspirates from, even with experienced operators.

Core needle biopsy offers an alternative method that may be more effective in improving the accuracy of diagnosis of these challenging nodules, especially in centers that may have to conduct smaller number of cases and lacking the other supportive laboratory facilities, experiences, or expertise to consistently obtain high adequacy and accuracy rate for aspiration alone. The cases in which it is difficult to obtain an adequate diagnosis with an aspirate are not the same as those in which it is difficult to obtain an adequate diagnosis with a core.[19]That is, in many cases, the difficulty in obtaining adequate material rests with the lesion itself, not necessarily with the skill of the operator. In such cases, core needle biopsy seems to be a more effective strategy to try to obtain adequate material from a nodule that is difficult to aspirate. An analysis of data shows that non-diagnostic and inconclusive rate of CNB have been reduced significantly as these were more in previous studies.[20]The present study suggests that non-diagnostic and inconclusive rate of subsequent CNB are much lower than repeated FNA results which were also observed in previous analysis of some studies, those were 6.4% and 3.3% to 16.1% by CNB, much lower than in repeated FNA (36.5%,29.9% to 43% respectively).[21] Many authors were reluctant to use core biopsy for preoperative assessment of thyroid nodule due to many complications,[22] but recent advancement of various instruments and techniques minimized it.Suh et al reported that CNB had a nondiagnostic rate of 1.3% and an inconclusive result rate of 5.9%, and a high diagnostic accuracy of 97.6% with a negligible complication rate of 0.2%.[23]

Previous studies have noted a low but increased incidence of bleeding complications associated with core needle biopsy.[20.23]None of those complications resulted in the need for hospitalization. In our present study, no complication of clinical significance was observed, although the incidence of bleeding and hematoma with core needle biopsy may be higher than with FNA. There is no question that an operator may take as many as 12 passes at a nodule with a fine needle to get diagnostic tissue, in contrast, the core needle biopsy was always with only 1 pass.

Limitations of the study

The study was conducted in two hospitals with small sample size. So, the results may not be reflected to the whole country.

V. Conclusions:

Overall, our results suggest that there is an important role of core-needle biopsy in preoperative assessment of thyroid nodule. In the settings in which fine needle aspiration is difficult and yield can not be improved by increased education and training, the core needle biopsy offers an alternative technique. Core needle biopsy has more adequacyand accuracy rate than that of FNA. Although, the combination of the two tests has the highest usefulness.

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