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Fine Needle Aspiration Cytology Utility in Neoplastic Thyroid Lesions

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Abstract

Fine needle aspiration cytology (FNAC) is a valuable adjunct to pre-operative screening in the diagnosis of thyroid nodules and has emerged as one of the well-established first-line diagnostic techniques. In most cases, it can distinguish between benign and malignant lesions. FNAC is a rapid, efficient, cost-effective, relatively painless procedure with a high diagnostic accuracy. It has high rate of sensitivity and specificity in diagnosing thyroid neoplastic lesions. Purpose of this study was to evaluate the effectiveness of FNAC in the diagnosis of neoplastic thyroid lesions and confirmation of the diagnosis by histopathological study and report the malignancy risk for FNA of thyroid lesions. The present study was carried out in our institute during the January 2012 to September 2016. This study was a retrospective study and a comparison was drawn between FNAC results and final histological diagnosis. In our study, 745 cases of thyroid FNAC smears were analyzed and cyto-histopathological correlation was done in 39 cases of neoplastic lesions. 33 cases werediagnosed as neoplastic lesions by FNAC. The overall surgical yield of malignancy by FNAC was 26.84%. In our study, FNAC diagnosis had 79.84% sensitivity, 97.6% specificity, 6.06% false positive rate, 8.9% false negative rate, and 91.86% accuracy. Hence, FNAC has been proven to be an efficient and guide the clinical treatment of patients with thyroid nodules.

Keywords: Cyto-Histopathological Correlation; Fine Needle Aspiration Cytology; Thyroid Neoplastic Lesions; Accuracy.

Introduction

Fine needle aspiration cytology (FNAC) was first described in the 1930's by Martin and Ellis [1].Thyroid nodules are common clinical findings and have a reported prevalence of 4–7% of adult population. However, fewer than 5% of adult thyroid nodules are malignant, and the vast majority is non-neoplastic lesions. The distinction of benign neoplastic lesions from malignant nodules cannot be based reliably on the clinical presentation alone [2]. Now FNAC of the thyroid gland is a well-established, first-line diagnostic test for the evaluation of diffuse thyroid lesions as well as of thyroid nodules with the main purpose of confirming benign lesions [3]. Most solitary nodules are benign, but they are usually the first sign of thyroid cancer [4]. FNAC is a simple, rapid, and cost-effective test that can effectively distinguish between neoplastic and non-neoplastic lesions of the thyroid. It can effectively triage patients with neoplastic thyroid nodules as to who require surgery and who do not [5]. Our study is based on cytological diagnosis of thyroid lesions and it's histopathological correlation. It bridges the communication gap between clinicians and pathologists and thus helps the surgeons to take appropriate therapeutic interventions [6].

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Materials & Methods

The present retrospective study was carried out in our institute from January 2012 to September 2016. The study comprised of 745 patients who presented with the history of swelling of thyroid which were referred from the Departments of Surgery, Medicine & ENT. The cases and notes were retrieved and information about the age, sex, ultrasound findings,

cytological and histological diagnoses was reviewed. The aspirate was satisfactory for interpretation in majority of cases. It was blood mixed to frankly hemorrhagic and in some cases, either brown or dark brown fluid was aspirated, ranging from 1 to 8 mL.In cases of cystic lesions, fluid was completely aspirated and was centrifuged. Subsequently sedimented material was examined. Re-aspiration was done in such cases. Diagnosis of cytological smears was done according to standard criteria defined by various authors [2,5,6]. Hematoxylin-eosin, Papanicolaou and May-Grünwald-Giemsa (MGG) stainedslides were studied. We categorized our results into nondiagnostic or unsatisfactory for diagnosis, benign, follicular lesion of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, suspicious for malignancy, and malignant samples [5,6].

Inclusion Criteria

Cases, which were diagnosed as neoplastic by cytology and those cases diagnosed as nonneoplastic by FNAC but turned out to be neoplastic by histopathology.

Exclusion Criteria

Cases with inadequate material for interpretation.

The slides were reviewed in detail and labelled as below:

Adequate Sample

For a solid nodule, a specimen was considered adequate if it contained at least six well-preserved and well-stained follicular groups, containing at least ten cells. In contrast, abundant thick colloid, as found in a colloid nodule, did not have a requirement for a minimum number of follicular cells [7].

Non-Diagnostic or Unsatisfactory (ND/UNS)

A thyroid FNA sample is considered inadequate if it contains, fewer than six groups of well-preserved, well-stained follicular cell groups with 10 cells each and if the slide is poorly preserved, poorly stained or obscured follicular cells or if the thyroid FNA sample contains cyst fluid, with or without histiocytes, unsatisfactory owing to obscuring blood, overly thick smears, air drying of alcohol-fixed smears. These cytologic findings may also result from poor fixation, preparation, or staining or from excessive blood, necrotic material, or debris obscuring cellular details andhence misinterpretations [8].

Atypia of Undetermined Significance (AUS)

This diagnostic category is reserved for specimens that contain cells with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm (SFN), suspicious for a malignancy or malignant lesion. This category was subdivided into two microscopic descriptive subcategories. One subcategory was for cases wherein predominance of microfollicles seen in a sparsely cellular aspirate with scanty colloid. Another example, a smear that showed cytological features of high cellularity, tiny follicular cells arranged in sheets, clusters or singly, with occasional occurrence of multinucleated giant cells, and focal occurrence of Hurthle cells was described as atypical follicular lesion of undetermined significance. The other subcategory was for cases showing features suggestive of papillary carcinoma, including nuclear grooves, enlarged nuclei with pale chromatin, and alterations in nuclear contour and shape in an otherwise predominantly benign appearing sample [6,8].

Follicular Neoplasm/Suspicious for a Follicular Neoplasm

Refers to a cellular aspirate comprised of follicular cells, most of which are arranged in an altered architectural pattern characterized by significant cell crowding and/or microfollicle formation with scanty or no colloid (Fig. 1). The differential diagnosis included hyperplastic adenomatoid nodules, follicular adenoma, and follicular carcinoma. This category also included cases that demonstrated a predominant population of Hurthle cells which can be designated as Hurthle cell neoplasm (Fig. 2), which included hyperplastic adenomatoid nodule with Hurthle cell change, Hurthle cell adenoma, and Hurthle cell carcinoma [7,8].

Suspicious for Malignancy (SFM)

Belonged to the samples in which aspirates that had cytological features suggestive of, but not definitive of, papillary carcinoma, medullary carcinoma, or lymphoma were placed in this category. For example, an aspirate that had cytological features of high cellularity, comprised elongated oblong cells with occasional plasmacytoid appearance with some cells showing Hurthle cell change and possessed a matrix different from colloid, possibly amyloid, was classified as suspicious for medullary carcinoma. It also includes benign follicular cells admixed with cells that have nuclear enlargement, pallor, grooving, nuclear molding/irregularity in a sparsely cellular

smear with any evidence of cystic degeneration based on the presence of hemosiderin laden macrophages. If only 1 or 2 characteristic features of papillary carcinoma thyroid are present, or if they are only focal and not widespread throughout the follicular cell population, a malignant diagnosis cannot be made with certainty. Such cases are best classified as "suspicious for malignancy" [6,7,8].

Positive for Malignancy

This category applied to thyroid FNA smears that showed unequivocal evidence of malignant neoplasm that included papillary carcinoma of thyroid and its variants, medullary carcinoma, anaplastic carcinoma, lymphoma, and metastatic tumors [6,7,8].

Cyto-Histopathological Correlation

After categorization, FNAC results were compared with the definitive histopathological diagnosis which was considered as the gold standard. Cases with cytohistological disparity were selected and reevaluated for the detection of possible cause. This was done in 39cases. Thereby, we could calculate the sensitivity, specificity, diagnostic accuracy, false positive value (FPV) and false negative value (FNV) of FNAC in diagnosing thyroid lesions.

Results

Based on a cohort of 745 thyroid FNAs, in the present study, the age of patients ranged from 12 to 78 years, with median age of 42 years. There was a female predominance giving a female-to-male ratio of 5.4:1. 11.40% of the thyroid nodules were classified as unsatisfactory, 84.02% benign; 0.13% Atypia of undetermined significance; 1.74%, suspicious of follicular neoplasm; 0.13%, suspicious of malignancy and 2.55%, positive for malignancy (Table 1). In our series, analysis of statistics data revealed (Table 2) a sensitivity of 79.48%, specificity of 97.64%, and diagnostic accuracy of 91.86%. The overall accuracyof cytologic diagnosis in our study was 91.86%.With the available data, the calculated false negative (FN), and false positive (FP) rates were 8.9% and 6.06% respectively.

Discussion

Fine needle aspiration cytology is regarded as the gold standard initial investigation in the diagnosis of thyroid swellings. The technique is safe, simple and quick with a low complication rate. Several other tests, such as high resolution ultrasonography, radioisotope

Table 1: Distribution of cases according to cytologic diagnosis

Cytologic diagnosis	No.	Percentage
Benign	626	84.02
Follicular lesion of US	01	0.13
Follicular neoplasm	13	1.74
Suspicious of malignancy	01	0.13
Malignant	19	2.55
Unsatisfactory	85	11.40
Total	745	100

Table 2: Relations between cytologic and final diagnosis by biopsy in calculations of false negative and false positive rates

		Biopsy Diagnosis		
		Positive	Negative	Total
FNAC Diagnosis	Positive	31	2	33
	Negative	08	82	90
	Total	39	84	123

Table 3: Comparison of FNAC results of present study with Lee et al study

Cytologic diagnosis	Present study (in %)	Lee et al study (in %)
Benign	84.02	67.7
Follicular lesion of US	0.13	3.1
Follicular neoplasm	1.74	1.1
Suspicious of malignancy	0.13	5.1
Malignant	2.55	13
Unsatisfactory	11.40	10

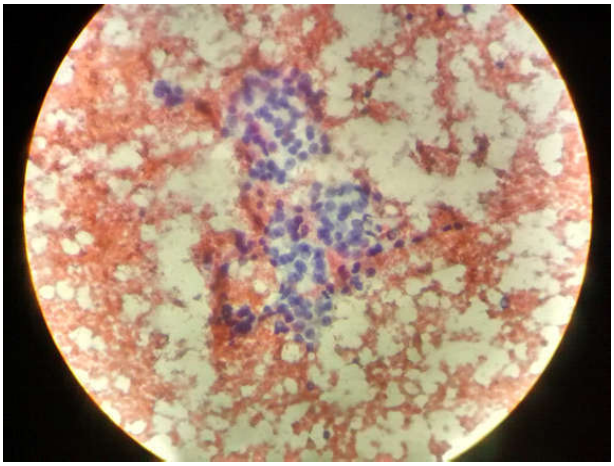

Fig. 1: Cellular smear of follicular neoplasm: Cells arranged in three dimensional cluster, microfollicular pattern, attempt at acinar arrangement and cells with mild anisokaryosis and high N/C ratio (H and E, × 400)

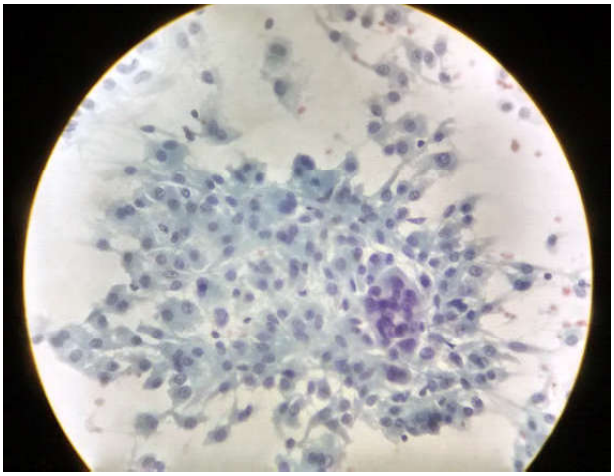

Fig. 2: Hurthle cell neoplasm: Cellular smear with sheets of oxyphilic cells having abundant granular cytoplasm and eccentrically placed nucleus (Pap,× 400)

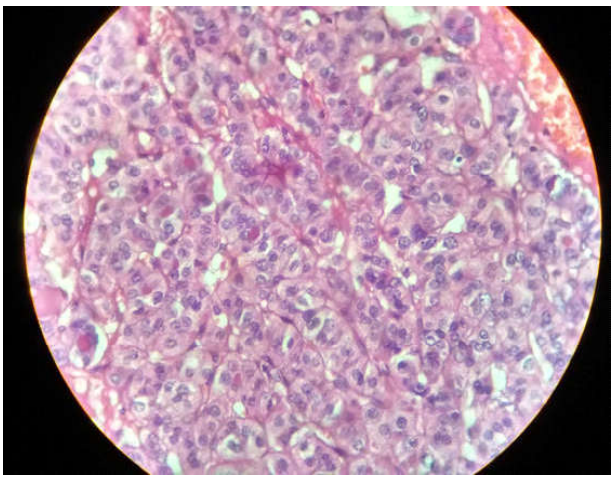

Fig. 3: Histopathological findings of Hurthle cell: Sheets of oxyphilic cells having abundant granular cytoplasm and mild anisonucleosis features (H & E, × 400)

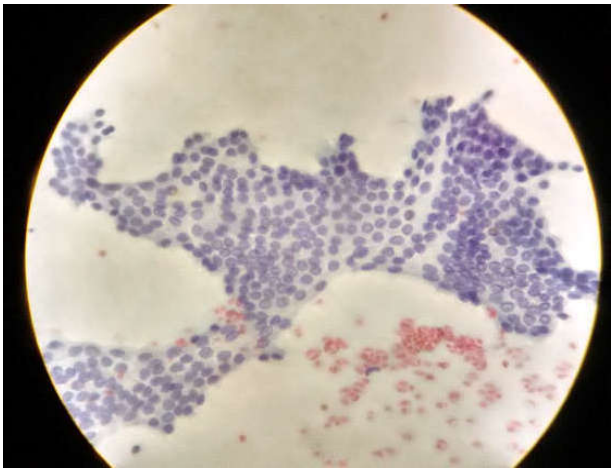

Fig. 4: Photomicrograph of a smear categorized as papillary carcinoma. Thyroid follicular cells arranged in papillae with distinct anatomical borders (Pap, ×400)

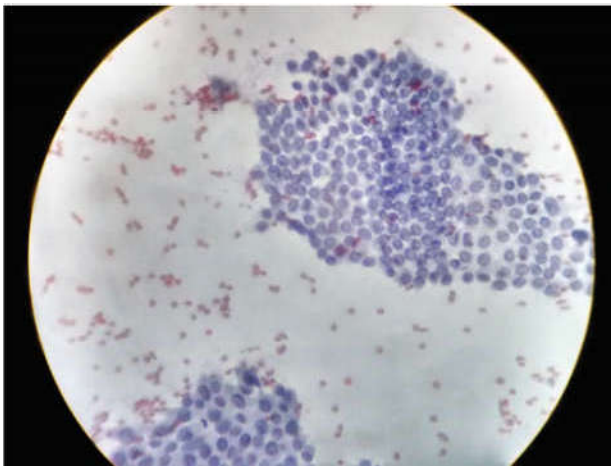

Fig. 5: A case of papillary carcinoma featuring syncytial arrangement of cells with prominent nuclear grooves. The nuclei show ground glass chromatin, intranuclear cytoplasmic inclusions (Pap, ×400)

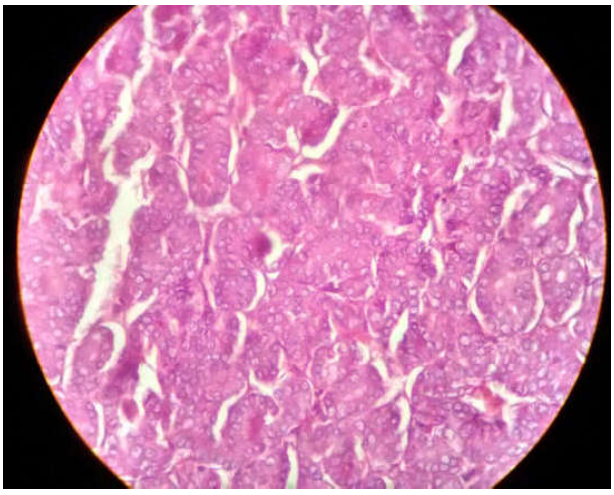

Fig. 6: Tumor cells arranged in follicular pattern with cells showing nuclear features of follicular variant of papillary carcinoma in biopsy findings (H & E, × 400)

scanning and others have been used for evaluation of thyroid swellings before proceeding to thyroid surgery [9]. However, FNAC is still regarded as the single most accurate and cost-effective procedure, particularly if ultrasound is used as a guide for better sample collection, especially for cystic lesions [10]. It has greatly improved the clinical management of thyroid nodules. Hence, every thyroid FNA must be evaluated for adequacy [8]. Nevertheless, like any other test, FNAC has its limitations and diagnostic pitfalls. These limitations include false negative and false positive results and a proportion of FNA results that are not obviously benign or malignant and fall into the indeterminate or suspicious group [11]. The reported pitfalls are those related to specimen adequacy, sampling techniques, the skill of the person performing the aspiration, the experience of the pathologist interpreting the aspirate and the overlapping of cytological features between some benign and malignant thyroid lesions[12]. The indeterminate diagnosis of follicular neoplasm encompasses a number of heterogeneous thyroid lesions including cellular adenomatoid nodule, follicular adenoma, and follicular carcinoma [7]. Additionally, the interpretation of follicular variant of papillary carcinoma (FVPC) in cytology may be difficult when prominent classic nuclear features of papillary thyroid carcinoma are absent [4]. Another limitation of FNAC is the presence of false negative and positive results particularly with small tumors and when there is associated degenerative or inflammatory change in adjacent thyroid tissue. In addition, there is a group of lesions which overlap between benign and malignant features. For instance, the distinction between a cellular colloid goiter and a follicular neoplasm may be impossible [5]. With these points, we conducted a retrospective study of fine needle aspiration cytology utility in neoplastic thyroid lesions in comparison with biopsy study.

In the present study, the age of patients, median age and female-to-male ratio was comparable with H. Gharib study [13]. Female to male ratio of present study for thyroid cancer is in agreement with the fact that thyroid cancer is commoner among women. It should also be noted that other study reported this ratio to be 2.5:1 [14]. Moreover, like Muratli *et al* [4], we found that on average male patients were diagnosed with malignancy at an older age than females were.

Sensitivity, specificity and diagnostic accuracy of our results were comparable with published data of J. Cap et al study, where FNAC of thyroid is reported to have a sensitivity ranges from 65% to 98%, a specificity of 72% to 100% [15]. The determinant factor for such a wide range of difference may be due to differences in number of cases, the included diagnostic categories, and how the cytopathologists classify 'suspicious', follicular lesion of undetermined significance, as well as false positive and negative samples [16].

The present study attempted to evaluate the efficacy of thyroid FNA results. Classified lesions of thyroid of present study as unsatisfactory, benign, atypia of undetermined significance, suspicious of follicular neoplasm, suspicious of malignancy and positive for malignancyresults were comparable with findings of (Table 02) Lee *et al*, study in which a similar retrospective study on 4966 thyroid aspirates was done and reported ND or unsatisfactory, 10%; benign, 67.7; Atypia of undetermined significance, 3.1%; suspicious of follicular neoplasm, 1.1%; suspicious of malignancy, 5.1%; and positive for malignancy 13% [17]. Accuracyof cytologic diagnosis in our study was similar to published data by Mundasad et al study where in an overall accuracy rate was around 95% in the detection of thyroid malignancy [18]. However, the interpretation errors in this study can be reduced by obtaining aspirates from different portions of the lesion, using ultrasound- guided FNA procedure, and reviewing slides by more than one cytopathologist [19]. More specifically, Pandey et al studies aimed to determine FNAC accuracy in diagnosis of thyroid cancer; however, it should be noted that FNAC cannot differentiate between benign and malignant follicular neoplasms. Further, definite differentiation between follicular adenoma and follicular carcinoma is only possible after thyroid lobectomy [20]. In addition, a Yang et al study of FNAC showed that 68% of the cases diagnosed by FNAC as follicular neoplasm turned out to be the follicular type of papillary carcinoma, indicating a considerable overlap between benign and malignant neoplasms [21].

With the available data, we calculated false negative (FN), and false positive (FP) rates. The false negative rate (FNR) is defined as the percentage of patients with benign cytology in whom malignant lesions are later confirmed on thyroidectomy. The false negative FNAC results may occur because of sampling error, coexistence of benign and malignant lesions, or cytomorphologic overlap between benign and low grade malignant tumors. This is of great concern because it indicates the potential to miss malignant lesion [22]. However, it is difficult to calculate the true false negative rate because only a small percentage (approximately 10%) of patients with benign cytological findings proceed to surgery. False negative rate ranged from 1% to 16% in different series [23]. In our series false negative rate was 8.90%, which agrees with that reported in literature. In the present study, eightcases were false negative and reported 05 cases

as hyperplastic nodule, as adenomatoid nodule and remaining one case as colloidnodular goiter. On biopsy examination of these cases proved to be as four cases of follicular adenoma, one case as follicular carcinoma and three cases of papillary carcinoma. These three cases of papillary carcinoma that were missed and diagnosed as hyperplastic nodular goiter. One of these cases was a nodule with cystic changes. It is worth noting that cystic changes may occur in neoplastic lesions, thus making it difficult to sample the solid portion of the tumor and in turn causing malignancy to be missed [20]. Many factors contribute to false negative diagnosis, but in our study, the key factor was the sampling error associated with the large size of nodules. A study of factors that lead to false negative diagnosis showed that there is a positive correlation between nodule size and the rate of false negative diagnosis [24]. More specifically, if a tumor is less than 1 cm in diameter (one of the false negative papillary carcinoma cases in our study was 1.4cm in diameter), sampling error is possible. Another case was diagnosed as hyperplastic nodule by FNAC and turned to be PTC by biopsy study.

The false positive rate (FPR) indicates that a patient with malignant FNAC result was found on histological examination to have benign lesion. In our series the false positive rate was 6.06% which agrees with other series that ranged from 0% to 8% [19]. In the present study, two cases were false positive. We reported one caseas follicular neoplasm and one as suspicious for papillary carcinoma that proved to be hyperplastic adenomatoid nodular goitre on histologic correlation. Similar or higher rates have also been reported, particularly for follicular neoplasm. Like Schreiner *et al* [25], we found adenomatoid nodules to be the main cause of poor histological correlation in the case of follicular neoplasm diagnosed by FNAC. Clumping and crowding of follicular cells may be seen if aspiration is performed on a hyperplastic nodule [26]. Among helpful criteria for the differentiation of hyperplastic adenomatoid nodule from follicular adenoma are follicular adenomas have higher and uniform cellularity, uniform nuclear enlargement, syncytial clusters, predominant microfollicles, and scanty colloid. Another point is that, like Pandey *et al*. [20] and Yang *et al*. [21], we found out that overemphasizing the presence of microfollicular structures or crowded cellular clusters in low-quality specimens may result in FP diagnosis. Concerning false positive results for papillary carcinoma, we can argue that although there are multiple cytological features that can be used for diagnosing this type of carcinoma, we cannot be sure that they are invariably available or sufficiently specific [27]. Furthermore, like Pandey *et al*., [20] we found the focal presence of some of the features mentioned above to be the cause of false positive diagnosis for papillary carcinoma.Moreover, some studies by Bagga PK, and Mahajan NC have reported higher rates of sensitivity and specificity than we observed in this research. This contradiction is because these studies dealt with a smaller number of cases and a lower percentage of malignancy [28]. In addition, in some studies, some or all of the undetermined or suspicious cases were excluded from statistical computation [29]. However, the problem is that this will lead to a reduction in the number of reported false negative and false positive cases and thus result in anexaggerated rate of accuracy [28]. Our study reports of FNRand FPR werein comparison with Chandanwale et al study [27]. It may be noted at this point that although follow-up observation of patients for at least a few years is necessary for determination of the true number of FN cases, this was not done in our study. Another limitation of this study is that we could not analyze some other features of thyroid cancer, such as risk factors and laboratory and imaging findings. The outcomes of the present study are important when considering the following:

Non Diagnostic or Unsatisfactory (ND/UNS)

It is, however, important to keep in mind that ND/UNS specimen does not mean negative specimen. Non-diagnostic or Unsatisfactory categories of present study (11.40%) correlated with Yassa et al. [30], and Nayar and Ivanovic [31] study. Jo et al [32], and Mufti et al [33], show higher percentage of Nondiagnostic categories. Layfield *et al*. emphasized that nodules with an initial ND/UNS result should be reaspirated after a recommended three months interval to prevent false positive interpretations due to reactive and reparative changes and also mentioned ultrasound guidance with immediate on-site adequacy evaluation is preferred for repeat aspiration after an initial ND/UN specimen especially for solid nodules reduces the false negative diagnosis [34]. According to Raab *et al*., cystic lesions with a nondiagnostic aspirate should undergo repeat FNAC [35]. In our study, one case that turned out to be malignant in ND/UNS category was of papillary carcinoma with cystic change. This type of papillary carcinoma of thyroid was being recognized as a possible cause for false negative thyroid FNAs [36].

However cellularity and adequacy are dependent not only on the technique of the aspirator but also on the inherent nature of the lesion.

Atypia of Undetermined Significance (AUS)

This recommended management for an initial AUS interpretation is the clinical and radiological correlation and for most cases, a repeat FNA at an appropriate interval. Layfield *et al*. reported that AUS is a heterogeneous category, which reflects the difficulty in the cytological diagnosis of the follicular lesions of thyroid. AUS is a category of last resort and should not be used discriminately and the frequency of AUS interpretation [34]. In our study was one case was diagnosed as AUS. The case diagnosed as AUS on FNAC was sparsely cellular consisting of monomorphic population of poorly cohesive small to medium sized cells with nuclear pleomorphism and high nuclear cytoplasmic ratio, which turned out to be nodular colloid goitre of thyroid. The less number of cases diagnosed as AUS in the present study could be explained by the strict adherence to diagnostic criteria and the cytopathologist's efforts in our practice setting to avoid ambiguity and keep the use of AUS to a minimum. Mondal et al. [37], and Mufti et al. [33], show much lower percentage because they gave strict adherence to diagnostic criteria and they also have large sample size.

Follicular Neoplasm/Suspicious for Follicular Neoplasm

It can be noted that in our study this category (1.74%) including Hurthle Cell Type was correlated with Nayar and Ivanovic [31], Mufti et al [33] studies. Mondal et al. [37], Yassa et al.[30], and Jo et al.[32], shows some higher percentage because of their large sample size and may be geographical distribution. The SFN category in our study yielded a malignancy rate of 15.38% which was quite comparable with other studies. In the present research, there were thirteen cases in the FN/SFN category.Histopathological confirmation (Fig. 3) was achieved in 8 cases and differed in 5 cases, which included 1 case each of Hashimoto thyroiditis, lymphocytic thyroiditis, hyperplastic nodule, follicular variant of papillary carcinoma, and Hurthle cell type of papillary carcinoma. The probable reasons for misdiagnosis of these cases was high cellularity with predominant follicular pattern. Review of histopathology showed presence of nodular hyperplasia with focal crowding of epithelium, and aspiration was probably done from these hypercellular areas and background of Hashimoto's thyroiditis in respective lesions. Hürthle cell metaplasia in addition to lymphocytic infiltration may show a mild to moderate degree of cellular atypia. Overemphasis on the cellularity that may be seen in this disease may lead us to categorize it as follicular neoplasm [20]. Suster *et al*, [38] Silverman *et al*, [39] Hall *et al*. [40] and Bommanahalli *et al*, [41] had similar observations in their study. One case of follicular variant of papillary carcinoma was misdiagnosed as follicular neoplasm because of high cellularity, predominant follicular pattern and nuclear overlapping. Focal nuclear features like grooving were ignored in view of predominant follicular pattern. As a matter of fact, there are multiple variants of papillary carcinoma, including the follicular variant, which may be wrongly diagnosed as follicular neoplasm. If the characteristic features of papillary carcinoma, such as true papillary structures or psammoma bodies are absent, the differentiation of papillary carcinoma from follicular neoplasm may be difficult given the fact that the nuclear changes of papillary carcinoma may be slight or focal, and also because features such as nuclear groove may be seen in other lesions, particularly in low-cellular smears [6]. Diagnosis of this tumor by FNAC and frozen section is notoriously difficult and unreliable. A possible remedy is multiple aspirations from different sites, and many feel that nuclear features in more than 20 cells have a greater risk of papillary carcinoma, and typical nuclear features are always helpful [39,40].

Misdiagnosis of follicular carcinoma as hyperplastic adenomatoid nodule in FNAC was because of high cellularity with follicular pattern and mild anisonucleosis. In well-differentiated follicular carcinoma, cellular atypia will be minimal and hence favors a benign lesion as suggested by Koss *et al* [42].They felt that nuclear enlargements were not helpful in differentiating follicular carcinoma from adenomas.

Moreover, less well-differentiated follicular carcinomas do not show marked nuclear atypia, but large nucleoli will be helpful. Following observations may be helpful indifferentiating adenomatous nodule and follicular neoplasm. As a general rule, smears from adenomatous nodule show less cells and more colloid than those from follicular neoplasm. In some rare occasions, confusing cellular smears are detected in non-neoplastic adenomatous nodules. In such rare cases, the presence of dispersed rather than tightly cohesive follicular cells is in favor of non-neoplastic adenomatous nodule. A possible remedy is multiple aspirations from different parts of the swelling that could demonstrate hypocellular, polymorphic, and colloid-rich areas. Demonstration of monolayered sheets of epithelial cells representing macrofollicles and degenerative changes would suggest the possibility of non-neoplastic lesions [43].Also, thyroid scintigram may solve this problem, where neoplastic nodules appear as cold nodules [44].

Suspicious for Malignancy

One case in our study showed suspicious for malignancy features. Nodules called suspicious for malignancies are resected by lobectomy or thyroidectomy. Most prove to be papillary carcinomas, and the rest are usually follicular adenomas [21,45]. The same general principle applies to other thyroid malignancies like medullary carcinoma and lymphoma, but these are encountered less frequently than PTC. Ancillary techniques immunohistochemistry, flow cytometry in borderline cases is usually more helpful with medullary carcinoma and lymphoma than with PTC [46].

Malignant Lesions

In this study 2.55% ofthe cases were malignant. This finding correlated with Muratli *et al* [4]. This has led to a reduction in the number of unnecessary surgeries and consequently to a rise in the percentage reported for malignancy [6].Three histological types of malignancy were observed in our study, indicating that FNAC is a valuable tool for diagnosing different types of malignancy. In addition, it should be noted that FNAC is a tool for separating cases that are in need of surgery from other cases.

Papillary Ca

In neoplastic lesions of 33 cases by FNAC, the percentages we observed for papillary carcinoma was 48.88%. FNAC diagnosis was offered in 16 cases (Fig. 4). Histopathological confirmation was available in 13 cases. In our study, the cytological smears of three cases wrongly diagnosed as papillary carcinoma.Of these, in two cases samples were moderately cellular showing numerous macrophages, thick colloid, cohesive clumps and sheets of follicular cells arranged in vague papillary patterns with nuclear overlapping and crowding. Few cells contained moderate amount of blue cytoplasm and round nucleus with pale open chromatin. Intranuclear inclusions were demonstrated in few cells. The histology showed features consistent with those of a hyperplastic adenomatoid nodule. In another case smears were cellular, arranged in papillary pattern with indistinct nuclear features. Misinterpretation of partly degenerated non-neoplastic follicular cells, focal papillary architecture, and intranuclear inclusions were probably the causes of error in these cases. Kini *et al*, [47] and Silverman *et al*, [39] had similar problems. Important features like intra-nuclear inclusions can be found in colloid goiter, medullary carcinoma and follicular adenoma [48]. Powdery nuclear chromatin, papillary fronds, intra-nuclear inclusions and nuclear grooves were common findings. Psammoma bodies are seen rarely [49]. Das *et al*, [50] suggested that "cystic papillary carcinoma" is a common cause for false negative reports in cytology. Small lesions of papillary carcinoma should be aspirated under imaging guidance [51].

Probable reasons for misdiagnosis of Papillary Ca by FNAC: Many thyroid cancers, especially papillary thyroid carcinoma, can be diagnosed with certainty by FNA. However, the nuclear and architectural changes of some PTCs are subtle and focal. This is particularly true for the follicular variant of PTC, which can be difficult to distinguish from a benign follicular nodule. Other PTCs may be incompletely sampled and yield only a small number of abnormal cells [52].

Other problems in diagnosing papillary carcinoma include cystic change, marked lymphocytic infiltration, mixed patterns of growth, papillary adenoma, hyalinizing trabecular adenoma and calcified debris [51]. Multiple samples collected from different parts of the lesion could help in proper diagnosis.

For cytodiagnosis of papillary thyroid cancer, the most important features suggested are intranuclear cytoplasmic inclusions, dense metaplastic cytoplasm, and papillary structures with distinct anatomical border (Fig. 5). These features can lead to a decrease in the wrong cytologic diagnosis of papillary thyroid carcinoma [53].

Two cases of a follicular variant of papillary carcinoma (FVPTC) in biopsy (Fig. 6) were also wrongly interpreted as follicular neoplasm. The smears had shown numerous follicular cells arranged in clusters, often with syncytial cell aggregates. There was prominent nuclear crowding and overlapping without any colloid.

The presence of follicular structures led to misinterpretation. A possible way to reduce such error is to do aspirations from different parts which could reveal the typical nuclear features of papillary carcinoma. A group of authors reported that papillary nuclear features in more than 20 cells would have a greater risk of occurrence of papillary carcinoma, although these findings may also lead to over interpretation [45].

Hurthle Cell Ca

One case of Hürthle cell carcinoma was missed by FNAC and wrongly diagnosed as Hashimoto Thyroiditis. However, previous research has reported a lower percentage for this type of follicular carcinoma

or has failed to study it as a separate type of malignancy [54,55].

Medullary Carcinoma

No cases of medullary carcinoma were diagnosed by FNAC in our study.Hawkins *et al* findings for this carcinoma are tumor cells have plasmacytoid appearance with moderately pleomorphic nuclei, granular cytoplasm and occasional binucleated forms [56].

This can be missed in medullary carcinoma of giant cell type,in which it is cytologically identical to anaplastic carcinoma. Application of immunostaining for calcitonin, or electron microscopy can solve the problem [57].

Anaplastic Carcinoma

One case of anaplastic carcinoma was suspected in which fnac sample was highly cellular with marked pleomorphism. Clusters of round to spindle-shaped tumor cells having hyperchromatic nuclei with mitotic figures. As patients was not available for further followup, diagnosis was not confirmed by histopathology.

Zeppa *et al*, [58] stated that diagnostic reliability is limited, because these cases can be associated with inflammation, necrosis and hemorrhage.

Conclusion

FNAC of thyroid lesions is a safe, simple, cost-effective and accurate method for management of palpable thyroid lesions. It helps in determining the risk of malignancy, especially the importance of nuclear features in the diagnosis of papillary carcinoma and follicular variant of papillary carcinoma. Most cases of false positive diagnosis were in the follicular neoplasm/suspicious for follicular neoplasia.

Overemphasis on the presence of microfollicular structures was the main cause of false positive diagnosis. Taking samples from different regions of the nodule and fulfilling the criteria for adequacy and appropriateness can decrease the false negative rate. In addition, ultrasound and ancillary testing in the form of molecular genetics and immunocytochemistry can improve diagnostic accuracy.

In conclusion, the results of our study are comparable with the current published data and demonstrate that FNAC revealed a high specificity, acceptable sensitivity, and accurate initial diagnostic test for evaluation of patients with different types of neoplasia.

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