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Assessment of FNAC Using 23-Gauge Needle in the Diagnosis of Thyroid Lesions with Cyto-Histopathological Correlation

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ABSTRACT

Background: Thyroid diseases are among the commonest disorders of endocrine system worldwide. Fine needle aspiration cytology (FNAC) is the most reliable screening test and easy, cost-effective procedure in diagnosing thyroid lesions. **Objective:** to assess the frequency of Bethesda system diagnostic categories and correlation of FNAC results with histopathology. **Material and Methods:** This study was conducted on 634 thyroid FNA smears received between January 2015 and December 2019. Cytological findings were compared to histopathology in cases had surgical excision. **Results:** Out of 617 of thyroid FNAC smears, ND/US category comprised 129 (20.9%). 381 (60.7%) were diagnosed as benign; atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (AUS/FLUS) comprised 77 cases (12.5%). Follicular neoplasm (FN)/suspicious for follicular neoplasm (FN/SFN) included 11 (1.8%), 3 (0.5%) cases were diagnosed as SM, and 16 cases (2.6%) were within malignant category. Sensitivity, specificity, PPV, NPV and accuracy of FNAC were 82.8%, 94%, 88.9%, 90.4% and 89.9% respectively. **Conclusion:** FNAC is a highly sensitive and specific procedure in diagnosing different thyroid lesions thereby help in decreasing number of surgeries in benign lesions.

1. Introduction

Thyroid diseases are among the commonest endocrine disorders worldwide [1]. The prevalence of thyroid nodules is 3%–7% by palpation and 19%–67% by ultrasonography [2, 3], with annual increasing rates worldwide. Majority of thyroid nodules are benign, while thyroid cancer comprises 5% to 15% of thyroid nodules [4].

In Kingdom of Saudi Arabia (KSA) as well as in the Middle East region, thyroid lesions represent the most common endocrine diseases [5, 6]. In KSA, thyroid cancer accounted for about 11% of all newly diagnosed cancers, in 2008, in females. This was responsible for 6.1% of all newly diagnosed cancers in the year 2004 [5, 7].

Fine needle aspiration cytology (FNAC) of thyroid is minimally invasive, cost-effective procedure. It is markedly useful in identifying benign thyroid lesions and avoiding unnecessary surgery for patients with benign disease [8]. However, FNAC test has some limitations due to sampling errors, inadequate sampling, suboptimal preparation of the smears, and inter-observer variability in reporting smears, particularly in cases with equivocal cytological features. Furthermore, accuracy is lower in suspicious cytology and in follicular neoplasms [9, 10].

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was attempted in 2007 to report thyroid aspirates on basis of standardized terminology. It used six categories include; non-diagnostic ND/ unsatisfactory US (Bethesda system diagnostic categories, BDC I), benign (BDC II), atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) (BDC III), follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN) (BDC IV), suspicious for malignancy (SM) (BDC V), and malignant (BDC VI) [11, 12].

This study was conducted to analyze the thyroid cytology in accordance with Bethesda system, in addition to correlate cytological results with histopathology to estimate the FNAC accuracy in diagnosing different thyroid diseases.

2. Patients and Methods

This retrospective study was conducted on 617 thyroid FNA smears received at Pathology Department, King Fahad hospital (KFh), Al Baha city, between January 2015 and December 2019. Ethical approval was obtained from our institution ethical committee. FNAC technique was performed under ultrasound guidance using 23gauge needle by expert radiologists according to Kim criteria [13] that include the following criteria; FNAC of nodules with any single suspicious ultrasound feature, regardless of nodule size, is recommended. Kim defined the suspicious sonographic features as marked hypoechogenicity, microlobulated or irregular margins, presence of

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microcalcifications, and the ratio of anteroposterior to transverse diameter is of ≥ 1. Thyroid smears were fixed with Ethanol or air-dried methods and stained by Romanowsky or Papanicolaou stains, respectively. Two expert pathologists interpreted the aspirate using TBSRTC system.

On reviewing the file of all patients, we found 31% of these patients received either anticoagulant and 40% received salicylate as a prophylactic dose and these patients were asked to stop the anticoagulant or salicylate prior to FNAC.
After cytological diagnosis, one hundred patients were followed by thyroidectomy specimens. The obtained tissues were fixed in formalin. The samples were processed and stained in automatic tissue processor and Stainer. Hematoxylin and eosin (H&E) stained sections were examined by expert pathologists with cyto-histopathological correlation.

Assessment of FNAC test efficiency was performed after exclusion of ND/US and AUS/ FLUS cases, because those two categories do not yield definitive benign or malignant diagnosis. Furthermore, cases with histopathological diagnosis of incidental papillary carcinoma (PC) were excluded as they not aspirated by FNAC, and the smears were from coexisting benign lesions. Evaluation of FNAC efficiency was performed by calculation of sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), and negative predictive value (NPV).

Cases with cytological diagnosis of BDC IV, V, and VI and confirmed to be neoplastic by histopathology represented true-positive (TP) category, while those who turned out to be non-neoplastic represented false-positive (FP) results. The true-negative (TN) category included cases with BDC II and diagnosed non-neoplastic on histopathology, whilst those had neoplastic diagnosis were included within false-negative (FN) category.

The risk of malignancy (ROM) of different FNAC categories was estimated by comparing cytological findings with histopathologic results. It was calculated when; noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) and well differentiated tumor of uncertain malignant potential (WDT-UMP) were included in malignant cases and recalculated when NIFTP and WDT-UMP considered nonmalignant.

2.1. Statistical analysis

Data were checked, coded, entered and analyzed by using SPSS (The Statistical Package for Social Sciences) version 21.0 software and MedCalc version 19.0 software. Descriptive data are presented as means ± standard deviation for continuous variables and percentages for categorical variables. Receiver Operating Characteristic (ROC) curve measures the accuracy that combines sensitivity and specificity with the estimation of the area under the curve of FNA as regarding the histopathologic findings of study group. Statistical significance was set at p-value < 0.05.

3. Results

This study involved 617 of thyroid FNAC smears, those were taken from patients attending (King Fahad Hospital) in Al Baha city between 2015 and 2019. Biopsies were collected from patients aged between 15 and 94 years old; their mean age was 45.7±13.5 years. Patients aged between 20 to 60 years, were accounted for 86.6%. The majority (87.4%) was females and the male to female ratio was about 7:1. More than half of biopsies were collected from the left lobe (52.1%). Biopsies from the right lobe, isthmus and bilateral were 36.3%, 7.3% and 4.3% respectively (Table 1).

Out of 617 of thyroid FNAC smears, ND/US category BDCI comprised 129 (20.9%) cases. The smears were either paucicellular with colloid and RBC (9 cases), bloody (7 cases) paucicellular with mixed inflammatory cells (3 cases), with few crushed follicular cells (3 cases), or thick smear (2 cases), and 105 cases were labeled as unsatisfactory without specifying the cause (table 2). Benign category BDCII included 381 (60.7%) cases, 197 cases were benign follicular nodules, 99 cases of colloid nodule with cystic changes, 35 cases of colloid nodules,17 cases of dominant adenomatoid nodules, 5 cases of benign follicular nodules with Hurthle cell changes, 25 cases of Hashimoto thyroiditis, 2 granulomatous thyroiditis cases and one case of epidermoid cyst (table 2).

AUS/FLUS category comprised 77 (12.5%) cases. While FN/SFN included 11 (1.8%) cases, 3 Hurthle cell neoplasms, 1 favors carcinoma and 7 cases were not subcategorized. Three (0.5%) cases were diagnosed as SM, 1 favors PC, and 2 cases with no subcategory. As regards malignant category, they included 16 (2.6%) cases, eleven were classic PC, two were intracystic PC; two were follicular variant papillary carcinoma (FVPC), and 1 favors anaplastic carcinoma (table 2).

Only 1 hundred patients underwent surgery. Histopathological examination revealed 59 (59%) cases were non neoplastic lesions. Multinodular goiter (MNG) is the most common non neoplastic lesion (54 cases) including simple, toxic and MNG with adenomatous change. Four cases were Hashimoto thyroiditis, and one case was benign follicular nodule with Hurthle cell change (table 3) (figures 1).

The neoplastic cases included 12 (12%) cases of follicular adenoma (FA), 4 (4%) cases of follicular carcinoma (FC) (I angioinvasive, 1 minimally invasive, and 2 widely invasive), 2 (2%) cases were (WDT-UMP), 1 (1%) case was (NIFTP). Papillary carcinoma comprised the most common cancer 22 (22%) cases of (18 classic, 2 intracystic, and 2 microscopic) (table 3) (figures 2 and 3).

Six (4.7%) cases of ND/US category underwent surgery, five of them diagnosed MNG on histopathology and one case diagnosed PC. Fifty-four (14.2%) cases of benign category had undergone thyroidectomy. Forty-seven cases of them were confirmed to be non-neoplastic on histopathology (44 Goiter and 3 thyroiditis), therefore true negative FNAC findings were 47 (87%) cases. While 7 cases turned out to be neoplastic (2 FA, 1 NIFTP, 1 FC, 3 PC). After exclusion of 2 cases of incidental papillary microcarcinoma, the false negative results were 5 (9.3%).
Thirteen (16.9%) cases of AUS/FLUS had a follow-up surgery, four of them were diagnosed MNG by histopathology, while 5 cases were FA, 2 cases were FC, and 2 case PC. Surgery was done for 9 (81.8%) cases of FN/SFN category. Seven cases were proved to be neoplastic on histopathology (5 FA, 1 WDT-UMP, and 1 FC) and those represent true positive results (77.8%). While 2 cases were diagnosed MNG, and those considered false positive (22.2).

All 3 (100%) cases of SM category underwent surgical intervention. Two cases of them confirmed to be malignant (PC) and they represent true positive results (67%). While one case not proven, had thyroiditis, and considered false positive finding (33%). Fifteen malignant (93.8%) cases were followed by

surgical excision, all of them were proved to be neoplastic/malignant (1 WDT-UMP and 14 PC). Therefore, true positive results were (100) in this category (table 4).

The risk of malignancy was estimated in each Bethesda system diagnostic category. When NIFTP and WDT-UMP included in malignant cases, the ROM was 16.7% for BDC I, 11.1% for BDC II, 30.8% for BDC III, 22.2% for BDC IV, 66.7% for BDC V, and 100% for BDC VI. While, when NIFTP and WDT-UMP included in nonmalignant neoplasms, the ROMs were 16.7%, 7.4%, 30.8%, 22.2%, 66.7%, and 93.3% respectively (table 5).
Based on cyto-histopathological comparison, the ROC plots curve calculated the sensitivity, specificity, PPV, NPV and accuracy of FNAC after exclusion of ND/US, AUS/FLUS categories. Furthermore, the two cases of incidental papillary microcarcinoma were excluded. The parameters were 82.8%, 94%, 88.9%, 90.4% and 89.9% respectively.

4. Discussion

Thyroid diseases are misunderstood and are often overlooked and misdiagnosed [14] however, in most western countries the real problem has to do with the overdiagnosis and overtreatment. FNAC is a rapid, cost-effective, and easy procedure with few complications. It is also markedly useful in diagnosing thyroid nodules as benign or malignant, and subsequently reducing unneeded surgery in benign lesions [11, 15].

Yet, FNAC has limitations due to scanty sample, variation in sampling technique, skills of the technique performer, the experience of cytologist, and vascularity of thyroid swelling. All those limitations impede reporting accurate diagnosis [16]. Thereby, our study was conducted to estimate the accuracy of FNAC test in identifying different thyroid lesions through correlation of FNA with histopathological diagnoses.

Two major systems were applied for FNA thyroid cytopathology reporting, the first of these was introduced by a National Cancer Institute (NCI) consensus conference in 2008, this system divided the thyroid nodule into seven-tiered categories: benign, Follicular lesion of undetermined significance (FLUS), Follicular neoplasm, Hurthle cell neoplasm, Suspicious for malignancy, Malignant and nondiagnostic. Each of these categories has a definite management ranging from follow/nothing, repeat FNA in 3 months, to hemithyroidectomy [16-19]. Another system is Bestheda system 2009 that was formally known as the "The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)"; it is based on the NCI classification of 2008. This system was subsequently widely implemented, has standardized diagnostic terminology [9], TBSRTC gave an approximated probability of malignancy for every cytology diagnostic type, and these have been used to develop management regulations for every type [17].

An updated version has been introduced in 2017 depending on the development in thyroid pathology field. In the new version of TBSRTC, the following highlights have been emerged; The ROM for each diagnostic category has been calculated when NIFTP is not included among malignancy. The risks of malignancy are displayed in the two ways: in the beginning, when NIFTP is not regarded as a malignancy, and another, when NIFTP is nevertheless encompassed amongst the “carcinomas.” The usual management of AUS/FLUS and FN/SFN now includes the possibility of molecular testing. The FN/SFN definition and the diagnostic clues have been modified considering NIFTP. Cases that exhibit mild nuclear changes in association with the papillary thyroid carcinoma are now considered. The definition as well as the diagnostic criteria applied for the papillary thyroid carcinoma subgroup of the malignant category have been changed to propose restricting the use to cases with “classical” features of papillary thyroid carcinoma. The optional education remarks may be used for the subsets of FN/SFN and SUS with cytomorphologic distinguishing characteristics reminiscent of FVPTC or NIFTP. An optional education remark can be used for “malignant; papillary thyroid carcinoma” cases to recognize that a small proportion may turn out to be NIFTP [18].

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) introduced a six-tiered diagnostic schematic presentation for thyroid Fine Needle Aspiration as follow: Benign, Atypia of Undetermined Signific ance/Follicular Lesion of Undetermined Significance (AUS/FLUS), suspicious for follicular neoplasm, suspicious for malignancy, malignant, and unsatisfactory with an aim to standardize diagnostic criteria. The most updated in the pathology of thyroid nodule is the proposed reclassification of the noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). This terminology suggestion was made in an attempt to decrease the overtreatment of apathetic thyroid nodules [18-21]. In 2015, the American Thyroid Association (ATA) applied updated recommendations specific for dealing with the thyroid nodules and approved the use of TBSRTC in order to achieve that objective.6 However, establishing the appropriate management for indeterminate nodules as atypia of undetermined significance, follicular lesion of undetermined significance and suspicious for follicular neoplasm/follicular neoplasm continues to be difficult. For these instances, molecular testing of aspirated material from thyroid nodules has been emerged [22-24].

In the current study, patients’ ages ranged from 15 to 94 years, the mean was (45.7±13.5) years, most of patients (86.6%) within range from 20 to 60 years. The male to female ratio was about 7:1. The findings are in accordance with other studies [10, 18, 19], as they reported that the majority of thyroid diseases were in female with middle age. More than half of smears, in our study, obtained from the left lobe (52.1%). On the contrary, Gupta et al., [10] showed that 60% of samples obtained from right lobe.
In the current work, FNAC interpreted 381 (60.7%) cases as benign. The most common benign diagnosis was benign follicular nodules (197) followed by colloid nodule with cystic changes (99). On histopathology, benign /non neoplastic lesions comprised most cases 59 (59%), and MNG is the most common non neoplastic lesion (54 cases). Many studies [10, 25, 26] reported similar findings.

In the present study, PC comprised the most common malignancy 22 (22%), on histopathology, and most of them were of classic type. In line with our results, Gupta et al., [10] and Zarif et al., [26] demonstrated that PC was the most common malignancy, but Zarif et al., [26] reported that FVPC was the most common subtype. Nandedkar et al., [25] contradicted the previous findings

and reported that FC was the common cancer in their study followed by PC.

Thyroid FNAC should be adequate, with well-preserved thyroid follicular cells to be properly diagnosed [27]. Adequacy criteria depend on the mode of aspiration (if under palpation or ultrasound guidance) as well as the nature of the aspirated lesion. It is difficult to obtain cellular aspirate from lesions with cystic changes, calcification, or sclerosis [25, 28]. TBSRTC has recommended a reaspiration of cases with BDCI after a minimum interval of 3 months to prevent false positive interpretations due to reparative or reactive changes [29]. Repeating FNAC is diagnostic in 50%–88% of cases; while, surgical excision should be done for cases with persistent inadequacy as the ROM is 10% [30]. In our study, ND/US category constituted 129 (20.9%) cases and this is comparable with Jo et al., [31] who reported (18.6%). Furthermore, in a meta-analysis of 8 studies by Bongiovanni et al., [32], the range of incidence of this category was from 1.8% to 23.6%, and the average was 12.9%. Much Lower percentages of this category were mentioned in other studies [25, 26, 32], they reported 4.3%, 6.4% and 11% respectively. The incidence of this category is dependent on the aspirator's experience [33]. Six (4.7%) cases of BDCI underwent surgical procedure, one case diagnosed PC, and the ROM was 16.7%. In accordance, Bongiovanni et al., [32] reported 16.8% ROM, while higher ROM (34.6 %.) was reported by Zarif et al., [26].FNAC results revealed 381 (60.7%) cases of benign BDC II. In accordance, many studies reported large percentages of this category from 59%, to 80% [32, 33, 34]. Abdulla et al., [33] reported slight lower rate of this category (55%) and they explained that because of selection bias. Benign category is usually managed by clinical follow-up, yet surgical intervention is performed for other concerns, cosmetic purposes, or pressure symptoms [25].

In the current study, fifty-four (14.2%) cases of BDCII had undergone thyroidectomy. Seven cases turned out to be neoplastic and the ROM was 11.1%, when NIFTP considered malignant and 7.4%, when NIFTP considered nonmalignant. Consistent with our findings, malignancy rates from 10.5%, to 15.6% were reported in other studies [25, 32, 34]. Lower malignancy rates were reported to be 0%–3% [9, 24]. Bongiovanni *e*t al., [32] displayed ROM range of 1%–10% with a 3.7% mean. These discordant findings were yielded when NIFTP, WDUM, or occult papillary carcinoma are included or excluded from malignant results. False negative results are those with benign/non neoplastic cytological diagnosis and turned out to be neoplastic on histopathology. False negative results represent a major source of limitation in using FNAC procedure, as many neoplastic cases would be missed without management. In the current cohort, after exclusion of the two cases of incidental papillary microcarcinoma, the false negative results were 5 (9.3%). Wide range of false negative rates was demonstrated by previous studies of 1.8-20% [10, 25, 27]. Coexistence of both benign and malignant lesions indicates the sampling from larger benign lesion not from adjacent malignant tissue as well as the overlap between low grade malignant and benign lesions, all those could yield false negative results [35][36]. Therefore, a negative FNAC diagnosis should never exclude malignancy in presence of obvious clinical suspicion, and cases with benign diagnosis should be followed up strictly [27].

AUS/FLUS diagnosis constitutes the most controversial category, as it yields inconclusive reporting. TBSRTC (2007) has recommended limitation in using BDC III to 7% or less [9]. While TBSRTC 2017 has extended the use of this diagnosis to 10% because of difficulty faced by many laboratories but ensured on using this diagnosis as the last option [24] The ROM for BDC III, is difficult to be recognized definitely because of small number of BDC III cases undergo surgery, those with repeated AUS/FLUS results or with suspicious clinical or sonographic findings [9].

In the present study, AUS/FLUS category comprised 77 (12.5%) cases. In accordance, Abdullah et al., [33] and Chakravarthy et al., [37] showed (16.2%) and (12%) respectively. Our result was much lower than the percentage (79.5%) reported by Chirayath et al., [38]. Thirteen cases (16.9%) within this category had a follow-up surgery and the ROM was 30.8%. In comparison, the malignancy rates of this category were ranged from15.9% to 29%, [25, 26, 32, 33]. Chakravarthy et al., [37], and Chirayath et al., [38] demonstrated much higher malignancy rates of 69% and 54.6% respectively. Hence, Chirayath et al., [38] recommended that patients of this category should be given strong consideration to surgery. FN/SFN category identifies a lesion that might be a follicular carcinoma and expose it for surrgical excision [38]. The recommended management for BDCIV is a diagnostic surgical lobectomy. Most resected specimens yield a diagnosis of follicular adenoma or adenomatoid nodule of MNG [23][24]. The current work included 11 cases (1.8%) within this category. In comparison, the published studies reported a range of 1.7%-20.3% [24], [25], [32], [33], [34][38-40]. In BDCIV category, malignancy risks of 15-30% and 25-40% were described by TBSRTC 2007 and TBSRTC 2017 respectively [9], [23], [24].

In our study, surgery was done for 9 (81.8) cases with 22.2% ROM. Alshaikh et al., [35] showed the same our percentage (22.2%) and Abdullah et al., [33] reported close result (27.3%). On the contrary, higher malignancy rates were showed by Chirayath et al [38] and Doodi et al. [41], 72.4%, and 81% respectively.

Three cases (0.5%) were diagnosed as SM by FNAC; close result (1.15%) was reported by Nandedkar et al., [25]. Many previous studies showed higher percentages of 2.6%- 7.2% [25, 27, 33, 34, 35]. All 3 (100%) cases of SM category underwent surgical intervention with 66.7% ROM. Previous studies had close rates of 75.2%, 76.2%, and 72.7% respectively [32, 33, 35]. Higher malignancy rates of 100% and 95.7% were reported in other studies [24, 25]. Ancillary studies have been suggested for SM category. Immunohistochemichal studies include pan-cytokeratin for anaplastic carcinoma, calcitonin, thyroglobulin, CEA, and chromogranin for medullary carcinoma, TTF-1 for metastatic carcinoma. These are to be done on cell block from FNA. Also, Flow cytometry is suggested for lymphoma. Moreover, genetic studies such as BRAF mutation or RET/PTC chromosomal rearrangements, for diagnosis of PC [42].

In the current cohort, sixteen (2.6%) cases were within FNA malignant category. This data is comparable with that reported in previous studies [24, 33- 35], as they reported rates of 1.98%, 2.2%, and 4.1%. Whilst Zarif et al., [26] and Sukumaran et al., [28] showed higher figures of 23.5% and 59.68% respectively. Fifteen malignant (93.8%) cases were followed by surgical

excision, all of them were confirmed histopathologically to be neoplastic/malignant (1 WDT-UMP and 14 PC). The malignancy rates were 100%, When WDT-UMP considered malignant and 93.3% When WDT-UMP considered nonmalignant. Many studies showed high reliability of FNAC procedure in identifying malignant lesions. As malignancy rates were reported to be 100% [25, 26, 28, 35] or 96%, and 98.6% [32, 33].

In our study, false positive results are those with cytologic diagnosis of FN/SFN, SM, or malignant but turned out to be nonneoplastic on histopathology. False positive finding comprised only 3 (3.8%) cases. In accordance, Nandedkar et **al.,** [25] reported false positive rate of 1.2% and Zarif et al., [26] showed (4.3%). Gupta et al., [10] reported high percentage of 13.3%.

Sensitivity, specificity, PPV, NPV and accuracy of FNAC were calculated after exclusion of ND/US, AUS/FLUS categories. Furthermore, the two cases of incidental papillary microcarcinoma were excluded. The parameters were 82.8%, 94%, 88.9%, 90.4% and 89.9% respectively. Comparison between our parameters and those in previous publications is summarized in table (6).

To increase the accuracy of identifying the thyroid nodule, Marturano et al, [43] found a novel combined sonographic and elastosonographic parameter evaluation improved diagnostic accuracy for identifying thyroid nodules suspicious of malignancy. They studied the thyroid nodule imaging using five sonographic parameters (echogenicity, irregular margins, microcalcifications, intra-nodule blood flow and its irregularity) and two elastosonographic parameters (intra-nodule stiffness and its extension to adjacent tissue) and found that when the two procedures were analyzed separately, sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were 100%, 85%, 63% and 100% for ultrasonography and 60%, 92.5%, 67%, 90% for elastrosonography, respectively. When a combined sonographic and elastosonographic evaluation was introduced, the diagnostic accuracy was significantly improved (sensitivity 100%, specificity 92.55%, PPV 77%, NPV 100%).

In the current study we evaluated the FNAC in a single centre, and this considered as one of limitation of the study. A similar study done by Del Rio et al [44] who studied the correlation between BSRTC and real results in one center investigating the role of several factors as confounding factors for cytological diagnosis. The study was a retrospective study carried on 637 patients that underwent thyroid surgery in a single centre**.** They stated that the percentage of malignancy in category 2, 3 and 4 Bethesda's classes seem to be higher than those predicted by BSRTC. Also, they found a high rate of false positive considered as patients included in categories of suspected malignancy (Thyr 3-4-5-6) and thereafter resulted with benign pathology. This occurs specially in those patients with thyroiditis. In addition, they recommended more studies to evaluate real TBSRTC predictive value in single centres. At the same time, they found out that thyroiditis may be a confounding factor in cytological examination which would lead to an overstating of thyroid nodules.

The point of strength of this study is considered in its alignment with the recent updates in Bestheda system and its correlation with the cyto and histopathology in current situation. However, this study is a retrospective, and this consider as one of major limitation despite this, this study is considered as an initial screening for the efficacy of management protocol of thyroid lesions/nodule. In addition, it gives an idea about the integration and cooperation among disciplines especially the radiology, cyto/histopathology, and surgery.

5. Conclusion

Based on aforementioned results, despite false-negative and false-positive results, FNAC is a highly sensitive and specific procedure in diagnosing different thyroid lesions. Thereby, it can help in decreasing number of surgeries in benign lesions.

6. References

1. Hall JE, GuytonAC(2011):Guyton and Halltextbook of medical physiology. Philadelphia,PA,Saunders. Elsevier, http://www.clincalkey.com/dura/browse/.
2. Hegedus, L. The thyroid nodule.N. Engl. J. Med.2004,351, pp. 1764–1771.
3. Tan, G.H.; Gharib, H. Thyroid incidentalomas: Management approaches to nonpalpable nodules discovered incidentally on thyroid imaging.Ann. Intern. Med. 1997, 126, pp. 226–231.
4. Jemal, A.; Siegel, R.; Xu, J.; Ward, E. Cancer statistics, 2010.CA Cancer J. Clin. 2010 ,60, pp. 277–300.
5. Albasri A, Sawaf Z, Hussainy AS, Alhujaily A. Histopathological patterns of thyroid disease in Al-Madinah region of Saudi Arabia. Asian Pac J Cancer Prev. 2014; 15(14), pp. 5565-5570.
6. Al Shahrani AS, El-Metwally A, Al-Surimi K, Bin Salih S, Saleh Y, Al-Shehri A, Ali A. The epidemiology of thyroid diseases in the Arab world: A systematic review. J Public Health Epidemiol. 2016; 8, pp.17-26.
7. Refeidi AA, Al-Shehri GY, Al-Ahmary AM, Tahtouh MI, Alsareii SA, Al-Ghamdi AG, Mahfouz AA, et al. Patterns of thyroid cancer in Southwestern Saudi Arabia. Saudi Med J. 2010; 31(11), pp. 1238-1241.
8. H. H. Wang, "Reporting thyroid fine-needle aspiration: Literature review and a proposal, "Diagnostic Cytopathology, vol.34, no. 1, pp. 67–76, 2006.
9. Cibas ES, Ali SZ NCI Thyroid FNA State of the Science Conference. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2009; 132:658–65.
10. Gupta M, Gupta S, and Gupta V B: Correlation of Fine Needle Aspiration Cytology with Histopathology in the Diagnosis of Solitary Thyroid Nodule. Journal of Thyroid Research, Volume 2010, Article ID 379051,5 pages.
11. Melo-Uribe MA, Sanabria Á, Romero-Rojas A, Pérez G, Vargas EJ, Abaúnza MC, et al. The Bethesda system for reporting thyroid cytopathology in Colombia: Correlation with histopathological diagnoses in oncology and non-oncology institutions. J Cytol. 2015; 32:12–6.
12. Wu HH, Rose C, Elsheikh TM. The Bethesda system for reporting thyroid cytopathology: An experience of 1,382 cases in a community practice setting with the implication for risk of neoplasm and risk of malignancy. Diagn Cytopathol. 2012; 40, pp. 399–403.
13. Kim EK, Park CS, Chung WY, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. *AJR* 2002; pp. 178:687.

14. Sarkis LM, Norlen O, Aniss A, Watson N, Delbridge LW, Sidhu SB, et al. The Australian experience with the Bethesda classification system for thyroid fine needle aspiration biopsies. Pathology. 2014; 46:592–5.
15. Esmaili HA and Taghipour H. Fine-Needle Aspiration in the Diagnosis of Thyroid Diseases:An Appraisal in Our Institution. Volume 2012, Article ID 912728, 4 Pages, ISRN Pathology.
16. Pandey P, Dixit A, Mahajan NC. Fine-needle aspiration of the thyroid: A cyto-histologic correlation with critical evaluation of discordant cases. Thyroid Res Pract 2012; 9:32-9.
17. Prathima S, Suresh TN, Harendra KM, Bhhaskaran A. Impact of the Bethesda system in reporting thyroid cytopathology. Thyroid Res Pract. 2016; 13:9–14.
18. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. J Am Soc Cytopathol. 2017; 6:217–22.
19. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol. 2016; 2:1023-1029.
20. Hirokawa M, Carney JA, Goellner JR, et al. Observer variation of encapsulated follicular lesions of the thyroid gland. Am J Surg Pathol. 2002; 26:1508-1514.
21. Lloyd RV, Erickson LA, Casey MB, et al. Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. Am J Surg Pathol. 2004; 28:1336-1340
22. Nikiforova MN, Wald AI, Roy S, et al. Targeted nextgeneration sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab. 2013; 98:E1852-E1860.
23. Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. J Clin Endocrinol Metab. 2014; 99:119-125.
24. Ferris RL, Baloch Z, Bernet V, et al; American Thyroid Association Surgical Affairs Committee. American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. Thyroid. 2015; 25:760-768.
25. Nandedkar SS, Dixit M, Malukani K, Varma AV, Gambhir S. Evaluation of thyroid lesions by fine-needle aspiration cytology according to bethesda system and its histopathological correlation. Int J App Basic Med Res 2018; 8:76-82.
26. Zarif H A[1], Ghandurah S E, Al-Garni MA, Sarah K B et al., , S Alsaywid BS, Satt MB: Thyroid nodules cytopathology applying the Bethesda system with histopathological correlation,Vol. 2, Issue 3; pp.143-148.
27. Sudilovsky D (2005) Interpretation of the paucicellular thyroid fine needle aspiration biopsy specimen. Pathol Case Rev 10:68–73.
28. Sukumaran R , Kattoor J, Pillai K R& Ramadas P T, Nayak N et al; Fine Needle Aspiration Cytology of Thyroid Lesions and its Correlation with Histopathology in a Series of 248 Patients. Indian J Surg Oncol (September 2014) 5(3):237–241.
29. L. J. Layfield, J. Abrams, B. Cochand-Priollet et al., "Post-thyroid FNA testing and treatment options: a synopsis of the national cancer institute thyroid fine needle aspiration state of the science conference," Diagnostic Cytopathology ,vol.36,no.6, pp.442–448,2008.
30. McHenry CR, Walfish PG, Rosen IB. Non-diagnostic fine needle aspiration biopsy: A dilemma in management of nodular thyroid disease. Am Surg. 1993;59:415–9.
31. Jo VY, Stelow EB, Dustin SM, Hanley KZ. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2010;134:450–6.
32. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology:A meta-analysis. Acta Cytol.2012;56:333–9.
33. Abdullah N, Hajeer M, Abudalu L, Sughayer M. Correlation study of thyroid nodule cytopathology and histopathology at two institutions in Jordan. *Cytojournal*. 2018;15:24. Published 2018 Oct 15. doi:10.4103/cytojournal.cytojournal_53_17
34. Mehra P. and Verma AK. Thyroid Cytopathology Reporting by the Bethesda System: A Two-Year Prospective Study in an Academic Institution, Pathology Research International.Volume 2015, Article ID 240505,11 pages
35. Alshaikh S, Harb Z, Aljufairi E, Almahari SA. Classification of thyroid fine-needle aspiration cytology into Bethesda categories: An institutional experience and review of the literature. *Cytojournal*. 2018;15:4. Published 2018 Feb 16. doi:10.4103/cytojournal.cytojournal_32_17
36. Bagga PK, Mahajan NC (2010) Fine needle aspiration cytology of thyroid swellings: how useful and accurate is it? Indian J Cancer 47: 437–442.
37. Chakravarthy NS, Chandramohan A, Prabhu AJ, Gowri M, Mannam P, Shyamkumar NK, et al. Ultrasound-guided fine-needle aspiration cytology along with clinical and radiological features in predicting thyroid malignancy in nodules ≥1 cm. Indian J Endocr Metab. 2018;22:597–604.
38. 38. Chirayath S R, Praveen V. Pavithran, Nithya Abraham, Vasantha Nair, Nisha Bhavani, Harish Kumar, Usha V. Menon, and Arun S. Menon; Prospective Study of Bethesda Categories III and IV Thyroid Nodules: Outcomes and Predictive Value of $BRAF^{V600E}$ Mutation, ndian J Endocrinol Metab. 2019 May-Jun; 23(3): 278–281.
39. Park H, Moon J, Yom C, Kim K, Choi J, Choi S, et al. Thyroid "Atypia of undetermined significance" with nuclear atypia has high rates of malignancy and BRAF mutation. Cancer Cytopathol. 2014;122:512–20.
40. Chandra S, Chandra H, Bisht S. Malignancy rate in thyroid nodules categorized as atypia of undetermined significance or follicular lesion of undetermined significance - An institutional experience. J Cytol. 2017; 34:144–8.
41. Doddi S, Chohda E, Maghsoudi S, Sheehan L, Sinha A, Chandak P, et al. The final outcome of indeterminate cytology of thyroid nodules in a District General Hospital. G Chir. 2015;36:122–7.
42. Filie AC, Asa SL, Geisinger KR et al., "Utilization of ancillary studies in thyroid fine needle aspirates: a synopsis of the national cancer institute thyroid fine needle aspiration state of the science conference," DiagnosticCytopathology, vol.36, no.6, pp. 438–441, 2008.
43. Marturano I, Russo M, Malandrino P, Buscema M, La Rosa GL, Spadaro A, Manzella L, Sciacca L, L'abbate L, Rizzo L.Minerva Endocrinol. 2020 Mar;45(1):3-11. doi: 10.23736/S0391-1977.19.02945-6. Epub 2019 Oct 11.PMID: 31625708.
44. Del Rio P, Cozzani F, Corcione L, Viani L, Loderer T, Rossini M. Correlation between cytological and histological findings in patients who underwent thyroidectomy. Predictive value and confounders. Minerva Endocrinol. 2019 Dec;44(4):357-362. doi: 10.23736/S0391-1977.18.02845-6. Epub 2018 Sep 24.PMID: 30256073.

Table 1: General characteristics of the studied thyroid biopsies

General characteristics	***The studied thyroid biopsies No = 634***	
	No	***%***
Age categories		
< 20 years	***4***	***0.6%***
20 – 39 years	***249***	***39.3%***
40 -59 years	***300***	***47.3%***
> 60 years	***81***	***12.8%***
Gender		
Male	***80***	***12.6%***
Female	***554***	***87.4%***
Year of specimen		
2015	***118***	***18.6%***
2016	***133***	***21%***
2017	***135***	***21.3%***
2018	***153***	***24.1%***
2019	***95***	***15%***
Site of the lesion in the thyroid		
Right lobe	***230***	***36.3%***
Left lobe	***330***	***52.1%***
Isthmus	***46***	***7.3%***
Bilateral	***28***	***4.3%***

Table 2: Distribution of cytological diagnoses of studied thyroid smears

Cytological diagnosis	The studied thyroid biopsies			
	No.	%	Sub-categorical diagnosis	No.
I. ND/US	129	20.9%	Paucicellular with colloid and RBCs Bloody smear Paucicellular with mixed inflammatory cells With few crushed follicular cells Thick smear No subcategory	9 7 3 3 2 105
II. Benign	381	60.7%	BFN Colloid nodule with cystic changes Colloid nodule DAN BFN with Hurthle cell changes Hashimoto thyroiditis Granulomatous thyroiditis Epidermoid cyst	197 99 35 17 5 25 2 1
III. AUS/FLUS	77	12.5%	No subcategory	-
IV. FN/SFN	11	1.8%	Hurthle cell neoplasms Favors carcinoma No subcategory	3 1 7
V. SM	3	0.5%	Favors (PC) No subcategory	1 2
VI. Malignant	16	2.6%	Favor (PC) Favor sintracystic (PC) Favor (FVPC) Favors anaplastic carcinoma	11 2 2 1
Total	617	100%		

ND/US; non-diagnostic/unsatisfactory, AUS/FLUS; atypia of undetermined significance/follicular lesion of undetermined significance, FN/SFN follicular neoplasm /suspicious for follicular neoplasm, SM; suspicious for malignancy, BFN; benign follicular nodule, DAN; dominant adenomatoid nodule, PC; papillary thyroid carcinoma, FVPC; follicular variant papillary carcinoma.

Table 3: Distribution of histological diagnoses in patients with thyroidectomy specimens

Histological diagnosis	No.	%	Subtype	No.
Non-neoplastic	59	59%	MNG Simple MNG Toxic MNG MNG with focal adenomatous changes Hashimoto thyroiditis BFN with Hurthle cell changes	33 10 9 2 4 1
Neoplastic				
Follicular adenoma	12	12%	-	- -
Follicular carcinoma	4	4%	Angioinvasive Minimally invasive Widely invasive	1 1 2
WDT-UMP	2	2%	-	-
NIFTP	1	1%	-	-
Papillary carcinoma	22	22%	Classic Intracystic Microscopic	18 2 2
Total	100	100%		

MNG; multinodular goiter, BFN; benign follicular nodule, WDT-UMP; well differentiated tumor of uncertain malignant potential; NIFTP; noninvasive follicular thyroid neoplasm with papillary like nuclear features.

Table 4: Correlation between cytotological and histopathological diagnosis in one hundred studied thyroid biopsies

Cytological diagnosis	Histological diagnosis							Total
	Non-neoplastic		Benign	Malignant				
	Goiter No (%)	Thyroiditis No (%)	Follicular adenoma No (%)	WDT-UMP No (%)	NIFTP No (%)	Follicular carcinoma No (%)	Papillary carcinoma No (%)	
I. ND/US	5 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.6%)	6
II. Benign	44 (80%)	3 (75%)	2 (16.6%)	0 (0%)	1 (100%)	1 (25%)	3 (13.6%)	54
III. AUS/FLUS	4 (7.3%)	0 (0%)	5 (41.7%)	0 (0%)	0 (0%)	2 (50%)	2 (9.1%)	13
IV. FN/SFN	2 (3.6%)	0 (0%)	5 (41.7%)	1 (50%)	0 (0%)	1 (25%)	0 (0%)	9
V. SM	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (9.1%)	3
VI. Malignant	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	14 (63.6%)	15
Total	55	4	12	2	1	4	22	100

Table 5: Risk of malignancy in each Bethesda system diagnostic category in relation to histological diagnosis in one hundred studied thyroid biopsies

Cytological diagnosis	Histological diagnosis	
	ROM when NIFTP and WDT-UMP considered malignant	ROM when NIFTP and WDT-UMP considered nonmalignant
I. UD/UNS	16.7%	16.7%
II. Benign	11.1%	7.4%
III. AUS/FLUS	30.8%	30.8%
IV. FN/SFN	22.2%	11.1%
V. SM	66.7%	66.7%
VI. Malignant	100%	93.3%

NIFTP; noninvasive follicular thyroid neoplasm with papillary like nuclear features, WDT-UMP; well differentiated tumor of uncertain malignant potential, ROM; risk of malignancy.

Table 6: Comparison between the present study parameters and the results in previous studies

Study	Publication	No. of cases	Sensitivity %	Specificity %	Accuracy %	PPV %	NPP %
Silverman et al., [36]	1986	309	93	96.5	-	88.9	96.5
Cusick et al ., [37]	1990	283	76	58	-	72	64
Altavilla et al., [38]	1990	257	71.4	100	-	100	94.4
Bouvet et al., [39]	1992	78	93.5	75	-	85.3	88.2
Ko et al., [40]	2003	207	78.4	98.2	-	99	66.3
Kessler et al., [41]	2005	170	79	98.5	-	98.7	98.7
Handa et al., [42]	2008	66	97	100	-	96	96
Gupta et al., [10]	2010	75	80	95	92	80	95%
Esmaili and Taghipour [14]	2012	1639	91.6	100	97	-	-
Abdullah et al.,[26]	2018	499	95.6	54.8	78.9	75.4	89.5
Nandedkar et al.,[18]	2018	606	85.7	98.6	97.7	-	-
Rout et al., [43]	2011	76	-	-	96.05	-	-
Zarif et al.,[19]	2018	408	88.9	75.6	81.5	79.7 %	84.4 %
Mehra and Verma [27]	2015	225	78.57	81.25	-	64.71	89.66
The present study	_	617	82.8%,	94	88.9	90.4	89.9

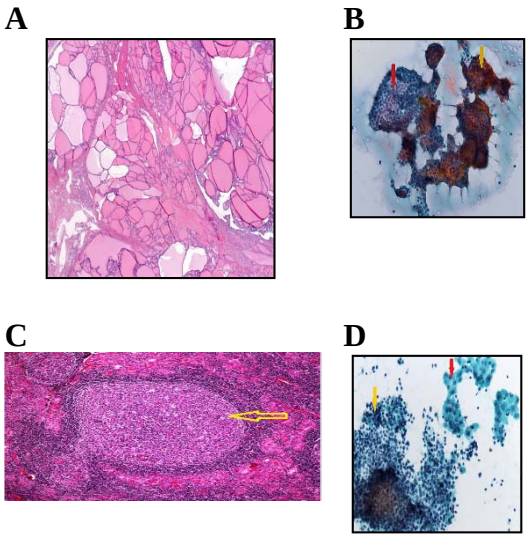

Figure 1. A, Multinodular goiter: Photomicrigraph displaying multiple nodules composed of variable size follicles lined by flattened epithelium. Secondary changes like fibrosis are seen (H&E stain, 40 x magnification). B, Multinodular goiter: Photomicrigraph displaying moderately cellular smears with xabundant thin or thick colloid (yellow arrow), sheets with evenly spaced follicular cells (red arrow) Smear, Papanicolaou stain, 40 x magnification). C, Hashimoto thyroiditis: Photomicrigraph displaying atrophic thyroid follicles with Hurthle cells and lymphoid follicles with germinal centers (H&E stain, 200 magnification). D, Hashimoto's thyroiditis: Photomicrigraph displaying clusters of oncocytic cells (red arrow) and many lymphoid cells (yellow arrow) (Smear, Papanicolaou stain, 40 x magnification).

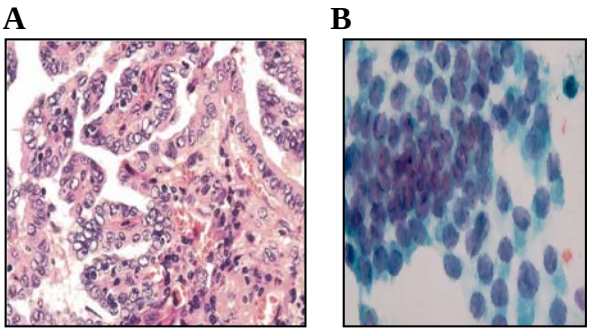

Figure 2. A, Papillary carcinoma: Photomicrigraph displaying nuclear features of papillary carcinoma: overlapping and chromatin clearing (H&E stain, 400 x magnification).
B, Papillary carcinoma: Photomicrigraph displaying sheet of tumor cells showing nuclear crowding with many cells displaying nuclear grooves (Smear, Papanicolaou stain, 400 x magnification).

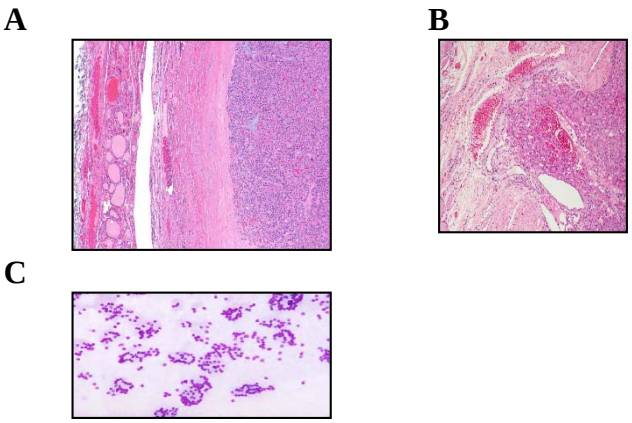

Figure 3. A, Follicular carcinoma: Photomicrigraph showing full thickness capsular (H&E stain,40 x magnification).B, Follicular adenoma: Photomicrigraph displaying follicular thyroid lesion Enveloped by thin fibrous capsule without invasion, the surrounded thyroid tissue shows sign of compression (H&E stain, 200 x magnification).C, Follicular neoplasm: Photomicrigraph displaying atypical follicular cell arranged in microfollicle, colloid is scanty (Smear, Papanicolaou stain, 40 x magnification).

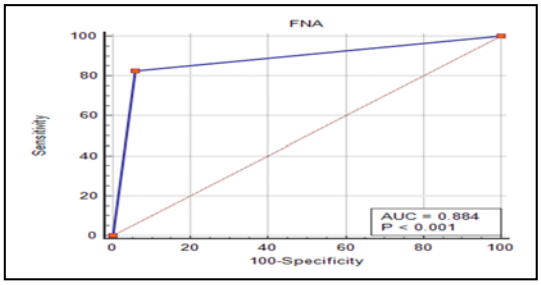

Figure 4. ROC plots curve of parameters measuring reliability of FNAC test (n =79) (AUC: Area under the curve, p-value <0.001).