

EFFICACY OF FINE NEEDLE ASPIRATION CYTOLOGY IN THE DIAGNOSIS OF THYROID LESIONS IN LIBYA

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Abstract

Objective: To assess the sensitivity, specificity and accuracy of fine needle aspiration cytology (FNAC) in the diagnosis of thyroid lesions, by comparing the results with histopathology diagnosis.

Methods: A retrospective study was conducted during years from 2006 to 2013. Patient data were collected and details of their thyroid lesion, including clinicopathological features and FNAC findings were recorded. A total of 200 patients, who had a clinically thyroid lesion were subjected to concurrent FNAC and surgical intervention.

Results: Out of total 200 patients, 51 cases had a FNAC that was unsatisfactory for evaluation. These patients were excluded from data analysis. The remaining 149 patients were included in the study. The results of the FNAC were compared with the tissue diagnosis obtained after surgical intervention. Out of 22 malignant lesions on surgical intervention, FNAC correctly diagnosed 12, and 9 were diagnosed suspicious, and the remaining one was misdiagnosed as benign cytology. So false negative being 1/22 (4.5%). Out of 66 patients diagnosed as follicular adenoma on histopathology results, FNAC picked 43 cases correctly as benign smear. The remaining 23 cases of follicular adenoma diagnosed on histopathology were reported as suspicious on FNAC, whereas, out of 61 goiter, FNAC diagnosed 57 as benign cytology, 4 case were suspicious as follicular neoplasia. The sensitivity and specificity of FNAC in the diagnosis of thyroid lesions were 95.5% and 78.7% respectively.

Conclusion: Thyroid cytology is an effective and rapid method in diagnosis of thyroid diseases. It helps in deciding which patient needs thyroidectomy. A negative cytology results does not exclude the possibility of malignancy, as there was a false negative rate of 5.4%.

Key Words: Thyroid mass, Fine needle aspiration cytology (FNAC), histopathology, thyroid cancer, malignant, benign, suspicious, unsatisfactory.

Introduction

Thyroid mass is a common public clinical problem for clinicians' radiologists and pathologists. Although, malignancy contribute a significant percentage of these palpable lumps, the most lesion of thyroid are benign (about 90%) and of no serious consequences, therefore the indications for surgery should be as accurate as possible [1, 2]. However, it is sometimes difficult to decide whether a suspicious lump is benign or malignant simply from clinical examination. FNAC has been routinely applied as a part of assessment of thyroid mass in combination with ultrasound-guided [3, 4, and 5]. Aspiration cytology allows an early diagnosis of thyroid diseases with good specificity and moderate sensitivity [6]. However, it cannot differentiate between follicular adenoma or carcinoma, and sometimes the diagnosis can only be done with reasonable uncertainty [7, 8].

In general, the ultrasound-guided FNAB is useful, simple, quick, highly reproducible, minimally invasive, and with rare false positive diagnoses [9, 10]. However, with this technique, false negative diagnoses (when a cancer cells may be missed) are possible in a few cases due to sampling error or too small number of cells examined. When expert radiologist used modern equipment, the false negative rate of fine needle aspiration biopsy (FNAB) was 1.5-11.5% [11,12,13, 14]. It has important and useful role to avoid unnecessary surgery, different old studies shows that ultrasound without FNAC have less than 50% sensitivity of all surgical removed thyroid nodules [15,16]. Recently, using ultrasound-guided FNAC increased the sensitivity ranging from 65% to 98%, whereas; the specificity ranges from 72% to 100%, with overall accuracy for cytologic diagnosis approaches 95% [6, 14, 16, 17, 18, and 19]. Over the years, this has led to a significant reduction in the number of unnecessary thyroidectomies that performed for benign lesions and at the same time, the rates of

cancer detected in surgically excised specimens increased[3, 4, 16,20,21, 22].US-FNA in the hands of experienced operators achieves high diagnostic accuracy. Recent American Association of Clinical Endocrinologists guidelines [22, 23], suggest selection of nodules for FNA based on US features, whereas the Society of Radiologists in Ultrasound recommends FNA for nodules larger than 1.0 cm in diameter [21]. This issue remains controversial.

Current study was conducted to determine the efficacy of an US-FNAB in diagnose of thyroid nodules by comparing with histopathology results. As well to evaluate some pathological features of thyroid tumors. To the best of our knowledge, there have been no reports from Libya that have figured the efficacy of an US-FNAB for thyroid nodules.

Material and Methods

The retrospective comparative study was performed on Libyan thyroid lesion samples. All cases were diagnosed and treated at Misurata Cancer Center and National oncology institute of Sabratha, Libya, during years from 2006 to 2013. Two-hundred patients with thyroid resections were performed during this period. Of these, 149 patients were included in the study in which preoperative FNAC and final histological diagnosis were available for review and compare. Patients' clinicopathological data were retrieved from the archives of pathology department.

Malignant ultrasonographic features including micro calcifications, marked solid hypoechogenic appearance, absent peripheral halo and irregular edges were considered [24].

Out of total 200 patients with thyroid lesions, 51 patients were had inadequate cytology and these cases were excluded from the determination of diagnostic indices. Of 149 thyroid diseases, lesions with benign cytology were regarded as a negative cytology for a malignancy, and lesions with

suspicious for a malignancy or definite malignant cytology were regarded as a positive cytology for a malignancy.

Fine Needle Aspiration Biopsy Technique

The 23-gauge was pushed toward the nodule under US screen. Usually, one pass was made through the abnormal area, however; if it was suspicious according to US malignant features (e.g. micro calcifications or nodule contour irregularity) then further passes were made in order not to miss the diagnosis. The aspirated cells are smeared on glass slides and immediately fixed with 95% ethanol, stained by haematoxylin and eosin, then to be examined by a cytopathologists. The procedure and response of FNAC investigation was often follow the guidelines of American Association of Clinical Endocrinologists. For instance, patients with multiple nodules, FNAC should performed with US, and selecting at least two nodules for FNAC when US features are suspicious. Recent thyroid nodule guidelines did not suggest routine rebiopsy of FNA-benign nodules [22, 23].

FNAC findings would generally be one of these four categories [6, 22, 23, and 25]:

Unsatisfactory (non-diagnostic). A definite microscopic diagnosis cannot be presented. The sample does not contain enough cells, often a specimen with less than six clusters of thyrocytes in all slides of the smear was considered as inadequate smear. On other hand, samples may also be not satisfactory because distortions due to fixation, defects in processing or laboratory performance.

Benign (negative). The lesion is not of serious concern in respect to cancer. Samples obtained from multinodular goiters, benign microfollicular adenoma, or normal thyroid are referred to as “colloid nodules” and show loosely cohesive sheaths of follicular epithelium, colloid, blood, and rare macrophages.

Suspicious (indeterminate). Probably malignant. This type of diagnosis requires additional investigations to determine the

nature of the lesion. Samples obtained from follicular/hurthle cell neoplasm (FN/HCN), cellular hyperplasia, or follicular variant of a papillary carcinoma. The lesion should be re-biopsied, with FNAC or open surgical intervention. Recently, the Bethesda system for reporting thyroid cytopathology classified FN/HCN in the independent category.⁷

Malignant (positive). The diagnosis can be considered certainly for cancer. Papillary carcinoma, the typically diagnostic cytology features are papillary configuration, large irregular nuclei, nuclear pseudo inclusion body and nuclear grooves. If only few feature with or without psammoma bodies then will be highly suggestive of papillary thyroid carcinoma. Less certainly, aspirates from a medullary thyroid carcinoma are hypercellular, composed of large, poorly cohesive cells, which are predominantly spindle shaped. Amyloid is often present. High-grade carcinoma can be also diagnosed cytologically, but distinguishing between primary and metastatic cancer is not easy.

Finally, the cytological outcomes were compared with the results of post-operative histopathological results. Data analysis was based on Galen and Gambino method, which calculates sensitivity and specificity of FNAC in differentiating between benign and malignant lesions (Table 1). The definition of false positive (FP) diagnosis in this study was the lesion of either suspected or definite malignancy in cytology, which was confirmed benign in the histopathology. Whereas, the false negative (FN) diagnosis was defined as the cytological specimen failed to diagnose a malignant lesions that are later confirmed on thyroidectomy. FNABs in relation to the sex, age, size of thyroid lesion were examined with special emphasis placed on the diagnosis of thyroid cancer.

Results

Out of total 200 patients with thyroid nodules (maximum diameter range, 0.5 to 6.0 cm; mean diameter, 3.4 cm). The

incidence of adequate specimens was 149 (74.9%) after the first US-FNAB, 51 patients had a FNAC that was either non-cellular or hemorrhagic smear. These patients were excluded from data analysis. The remaining 149 patients were included in the study (female: male = 122:27; mean age, 48.0 years; age range, 18 to 75 years). The results of the FNAC were compared with the tissue diagnosis obtained after the surgical intervention. Of 149 biopsies, the cytology was classified as benign for 101 lesions (67.8%), suspicious for a malignancy for 36 lesions (24.1%), and malignant for 12 lesions (8.1%), (Table 1). Out of 22 malignant lesions on

histopathology results, FNAC correctly diagnosed 12, and 9 were diagnosed suspicious, and the remaining one was misdiagnosed as non-malignant (Benign smear). So false negative being 1/22 (4.5%). Out of 66 patients diagnosed histologically as follicular adenoma, FNAC evaluated 23 cases as suspicious that revealed as follicular neoplasia, and the remaining 43 cases were reported by FNAC as benign smears. Whereas, out of 61 confirmed goiter, FNAC diagnosed 57 as benign smears and 4 cases were diagnosed as indeterminate cytological smears.

The sensitivity and specificity of FNAC was 95.5% and 78.7% respectively.

Table 1. Cyto-histopathological correlation of neoplastic and non-neoplastic lesions

Cytopathology	Histopathology			Total
	Non neoplastic disease	Benign tumor	Malignant tumor	
Malignant smear	0	0	12	12
Benign smear	57	43	1	101
Suspicious smear	4	23	9	36
Total	61	66	22	149

Table 2. Cyto-histopathological correlation of malignant and non-malignant lesions

Diagnosis		Histological	
		Malignant	Non malignant
FNA	Suspicious or malignant smear	(TP) 21	(FP) 27
	Benign smear	(FN) 1	(TN) 100

$$\text{Sensitivity} = \frac{TP}{TP+FN} = 21/22 = 95.5\%$$

$$\text{Specificity} = \frac{TN}{TN+FP} = 100/127 = 78.7\%$$

$$\text{Positive predictive value} = \frac{TP}{TP+FP} = 21/48 = 43.8\%$$

$$\text{Negative predictive value} = \frac{TN}{FN+TN} = 100/101 = 99.01\%$$

$$\text{Efficiency of test} = \frac{TP+TN}{TP+FP+TN+FN} = 121/149 = 81.3\%$$

When Galen and Gambino method is applied this gives 95.5% sensitivity of FNAC for reporting malignancy and 78.7% specificity to rule out malignancy. The positive predictive and negative predictive values 43.8% and 99.0% respectively. The overall accuracy in detecting malignant tumors was 81.3%.

Discussion

The importance of FNAC investigation in the diagnosis of thyroid tumors has been well established as this is a safe and cost-effective diagnostic procedure; the cost of FNAC is minimal, equipment is inexpensive and the technique is simple [9, 10]. Thyroid aspiration can be done anywhere, at the patient bed, at physician clinic. The most significant advantage of FNAC is the high degree of accuracy, rapid results, and a less invasive procedure than a tissue biopsy [9, 10]. FNAC of the thyroid can significantly reduce the number of needless thyroidectomies [3, 4, 16, and 20].

Of 22 malignant cases diagnosed on histology, 12 cases were diagnosed as malignant on both cytology and biopsy, 9 cases were diagnosed suspicious and 1 case was diagnosed benign on FNAC, which turned out to be malignant on surgical intervention, which represent the false negative rate (4.5%) in this study. Several studies have shown that false negative (FN) ranging from 1.5 to 11.5% [11, 12, 13, and 14]. This wide variation in frequency of false cytologic diagnosis may be due to different reasons including sampling errors and the interpretative errors by the cytopathologists; however, false-negative rates are lower in centers experienced with the ultrasonographic guiding biopsy techniques, and had expert cytopathologists [6, 12]. On other hand, the false positive (FP) results were 18.1%. Different studies have shown that false positive results, ranging from 0 to 8% [6, 12]. Although, still there is no agreement in which the cytopathologists

categorize suspicious, and how they define FP and FN results. Some authors include follicular lesions in the malignant/neoplastic category. Others categorize them in the negative group, and still others exclude them from the calculations altogether [29]. In current study, all indeterminate or suspicious cytology results of benign histology results were counted as false positive, this raised the rate of false positive in our study. In this study, out of 36 suspicious results 27 turned out to be benign and 9 malignant on excision biopsy, so the suspicious rate was (24%). This figure in line with international fraction range which are (10-30%) [6, 12].

FNAC is a valuable adjunct to pre-operative in the diagnosis of thyroid nodules, and in several cases, it can significantly distinguish between benign and malignant lesions [30]. One-hundred cases were found benign on both FNAC and biopsy, and 1 case diagnosed as benign on cytology turned out to be malignant on biopsy. The sensitivity, specificity and efficiency of fine needle aspiration cytology test in this study were 95.5%, 78.7 and 81.3% respectively, while in several studies, the sensitivity ranges from 65 to 98% and the specificity ranges from 72% to 100%. The overall accuracy for cytologic diagnosis approaches 95% [6, 12, and 16]. Small size of the tumor and certain histological types (follicular neoplasia and well-differentiated medullary carcinoma) may contribute to false negative results, and histologic evaluation of the nodule was necessary [28].

Thyroid ultrasonographic features associated with malignancy in thyroid nodules are micro calcifications, hypoechogenic, irregular margins or absent halo sign, solid aspect, these patterns, taken singly, are poorly predictive [2, 27].

In our study, the sonographic features support diagnosis of malignant lesion are including (hypoechoic solid lesion, echogenic with palpable regional lymph

nodes, and calcified echo spots less than 2 mm with acoustic shadowing). Whereas, the sonographic features that support diagnosis of benign lesion are including (pure cyst and normal echogenic). It clear in our institute the sensitivity and specificity of FNAC were raised up to 95.5% and 81.3% respectively after ultrasonographic malignant features were considered; for example re-aspirate the lesion from several directions.

Although, all unsatisfactory smears in current study were benign on histopathology results, the absence of malignant cells in an otherwise lack cellular smear does not exclude the malignancy.

Even though, FNAC has proven to be an effective diagnostic procedure in the evaluation of human thyroid lesions, and have a high degree of accuracy (81.3%), or more in some study [6, 12, 16]. There are some limitations to this application of FNAC analysis study [4, 11, and 13]. This is true even though FNAC estimations are sensitive methods with rate 95.5%. For instance, selection of examined areas of samples and the number of needle aspirates will affect the results to a considerable extent. Selections of sampling areas of study as well as the number of examined smears still require some subjectivity, which may affect the reproducibility of this investigation. In this study, the selection of examined areas and smeared cells were large enough to at least partly avoid this problem. Sampling methods affect comparison between different studies, and to a less extent within the same study. As a part of the efforts to introduce suitable sampling rules for these type of studies, the standard adequacy criteria of smear should be found at least 6 groups of follicular cells with a minimum of 10 cells in each group [7, 29]. A significant source of accuracy variation has been found because of different methodology. It is, however, greatly dependent on the standardization of laboratory methodology, including type of fixation and type of stains. Standardization

of thyroid surgery for example: the thyroid malignancies surgical intervention in this study were including total, subtotal and a lobectomy as well as regional lymph node resection was not performed for all of the malignant smears. On other hand, the technique of carrying out an US-FNAB of thyroid nodules is also not a standardized for all cases.

For these reasons, and because, this study was not a wide-ranging study, therefore the result of this current study should be confirmed by further wide-ranging study with more standardized preparation and interpretation of cytology samples.

Conclusion

The US-FNAB of thyroid nodules is an effective diagnostic method if achieved by an expert radiologist and cytopathologists. The sensitivity and specificity of FNAB in this study was 95.5% and 78.7%. FNAB is recommended for the diagnosis of thyroid lumps, however before going for definitive treatment, tissue diagnosis is necessary, as there have been cases of false negative results for FNAB.

Authors' Contributions

This work was carried out in collaboration between all authors. Author FA participate in the design and preparation of the manuscript and performed the statistical analysis. Author HG provided the clinical data, and participated in the organizing this data. Author AJ participate in the design, and coordinate the manuscript. Author JB conceived of the study, participate in the design, coordinate the research, and drafted the manuscript. All authors read and approved the final manuscript.

Consent

The Research Council of Misurata Cancer Center has approved the proposed study and publication of this research

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Competing Interests

Authors have declared that no competing interests exist.

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