

The Diagnostic accuracy of Ultrasound Guided Fine Needle Aspiration Biopsy for Dominant Nodules in Multinodular Goiter

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ABSTRACT

Background: FNAC is useful tool to evaluate dominant thyroid nodule in patients with multi nodular goiter however, because the diagnostic performance of US-based FNAC criteria varies according to the individual international society guidelines, clinicians should be aware of the strengths and weaknesses of US-based FNAC criteria in the management of dominant nodules in patients with multinodular goiter. FNAC is an office procedure, done with or without local anesthesia with 23 to 27 gauge needle, to obtain cells samples for cytological examination. It is a safe, accurate and cost-effective way for evaluating dominant thyroid nodules. **Objective:** the aim of this study was to discuss the accuracy of Ultrasound guided FNAC technique in diagnosis of pathological types of dominant nodule in multinodular goiter. **Patients and Methods:** this was a prospective study to evaluate the accuracy of FNAC in diagnosis of pathological type of dominant nodule in 20 patients with multinodular goiters who referred to the endocrine surgery unit at El-Demerdash Hospital, Ain Shams University from March 2017 to December 2017. **Results:** in our study the FNAC results indicated malignancy in 1 patients (5%), benign in 13 patients (65%) and intermediate in 6 patients (35%). The final histopathological diagnosis was malignancy in 3 of the patients (15%); one case had follicular thyroid carcinoma while two of the patients had malignant papillary thyroid tumor. Among the rest, 17 patients (85%) had benign lesion or tumor. Out of the 13 cases identified to be benign lesion by thyroid FNAC 7.7% of the group subjects were found to be malignant follicular carcinoma by biopsy (N=1). **Conclusion:** the main problem among the clinical features is false negatives, as it implies the presence of undetected carcinomas. Although FNAC is useful test, our decision making should not be depend on the basis of its results and sometimes clinical and U/S criteria are preferred to cytological data.

Keywords: Fluorodeoxyglucose, Fine-needle aspiration cytology, Ultrasonography, Magnetic resonance imaging

INTRODUCTION

Thyroid nodule is a discrete lesion in the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma ⁽¹⁾.

Thyroid nodules are common; their prevalence in the general population is high, the percentages vary depending on the mode of discovery: 2–6 % (palpation), 19–35 % (ultrasound) and 8–65 % (autopsy data) ⁽²⁾.

They are discovered either clinically on self-palpation by a patient, or during a physical examination by the clinician or incidentally during a radiologic procedure such as ultrasonography (US) imaging, computed tomography (CT) or magnetic resonance imaging (MRI) of the neck, or fluorodeoxyglucose (FDG) positron emission tomography. With the increased use of sensitive imaging techniques, thyroid nodules are being diagnosed incidentally with increasing frequency in the recent years ⁽³⁾.

Multinodular goiter (MNG) is defined as the palpation of multiple discrete nodules in the enlarged thyroid gland. Etiology and pathogenesis of MNG is not very clear. A mild dietary deficiency of iodine, slight impairment of hormones synthesis, increased iodide clearance from the kidney and presence of thyroid stimulating immunoglobulins have been suggested as the various causes ⁽⁴⁾.

MNG is a risk factor for epidemiologically ascertained thyroid malignancy. Epidemiologically studies have demonstrated the incidence of malignancy in patient with MNG was higher than the incidence of general population ⁽⁵⁾.

Traditionally patients with MNG have been considered less at risk of malignancy than those with single nodule. However, published reports show that the incidence of malignancy in patients with single nodule does not differ from those with MNG ⁽⁶⁾.

Initial assessment of a patient found to have a thyroid nodule either clinically or incidentally should include a detailed and relevant history plus physical examination. Laboratory tests should begin with measurement of serum thyroid-stimulating hormone (TSH). Thyroid scintigraphy/radionuclide thyroid scan should be performed in patients presenting with a low serum TSH ⁽⁷⁾.

Comprehensive history with focus on risk factors predicting malignancy should be part of the initial evaluation of a patient with thyroid nodule. Symptoms of hypothyroidism or hyperthyroidism should be assessed. Patients should be questioned about local pressure symptoms such as difficulty in swallowing or breathing, cough and change in voice ⁽⁷⁾.

Scintigraphy, a diagnostic test used in nuclear medicine, utilizing iodine radioisotopes (more commonly used; usually ¹²³I) or technetium pertechnetate (⁹⁹Tc), measures timed radioisotope uptake by the thyroid gland. The uptake of the radioisotopes will be greater in hyperfunctioning nodule and will be lower in most benign and virtually all malignant thyroid nodules than adjacent normal thyroid tissue ⁽⁸⁾.

Thyroid ultrasound should be performed in all those suspected or known to have a nodule to confirm the presence of a nodule, evaluate for additional nodules and cervical lymph nodes and assess for suspicious sonographic features. The next step in the evaluation of a thyroid nodule, if they meet the criteria as discussed later, is a fine needle aspiration (FNAC) cytology ⁽⁹⁾.

The recent ATA guidelines classify nodules into 5 risk groups based on US results. However, the current AACE guidelines suggest a more practical, 3-tier risk classification: low risk, intermediate risk and high risk thyroid lesions, based on their US characteristics ⁽⁷⁾.

The nodular characteristics that are associated with a higher likelihood of malignancy include a shape that is taller than wide measured in the transverse dimension, hypoechogenicity, irregular margins, microcalcifications, and absent halo ⁽¹⁰⁾.

The feature with the highest diagnostic odds ratio for malignancy was suggested to be the nodule being taller than wider. The more

suspicious characteristics that the nodule has, it increases the likelihood of malignancy. In contrast, benign nodule predicting US characteristics include purely cystic nodule (<2 % risk of malignancy) spongiform appearance (99.7 % specific for benign thyroid nodule) ⁽¹¹⁾.

AIM OF THE WORK

The aim of this study is to discuss the accuracy of Ultrasound guided FNAC technique in diagnosis of pathological types of dominant nodule in multinodular goiter.

Patients and Methods

This was a prospective study to evaluate the accuracy of FNAC in diagnosis of pathological type of dominant nodule in 20 patients with multinodular goiters who referred to the endocrine surgery unit at El-Demerdash Hospital in Ain Shams University from March 2017 to December 2017.

Patients selected were those who had MNG with prominent nodules who had US-guided FNAC and histology report. MNG patients were selected in whom FNAC had been indicated according to the ultrasound criteria of suspicious nodules which include:

A shape that is taller than wide measured in the transverse dimension, hypoechogenicity, irregular margins, microcalcifications, and absent halo.

Inclusion criteria: All patients with multinodular goiter and dominant nodule who are fit for elective surgical thyroidectomy, patients of age 18 -60 years, all patients should sign the informed consent.

Exclusion criteria: All patients younger than 18 and older than 60, patients who had previous thyroid operation, patient unfit for general anesthesia (untreatable coagulopathies, patient with severe cardiovascular or severe restrictive respiratory disease), and patients with vocal cord lesions.

The cytology study was carried out by cytopathologists expert in thyroid cytology.

The puncture technique consists of the following steps: Local disinfection of the puncture area with povidone iodine, Location of the suspected nodule by palpation; it was guided by ultrasound using the 'free-hand' technique, Injection of local anaesthesia,

Puncture with a Cameco syringe holder, using 20-ml disposable syringes and 22G-calibre needles, Suction was applied while the puncture was moved in the nodule to mobilize cell material. Once the aspirate had been obtained, aspiration was stopped and the needle removed. After aspiration a dry spread of the material was examined with May-Grünwald-Giemsa staining (Diff-Quick rapid variant). In the cases in which a papillary carcinoma was suspected, haematoxylin-eosin and/or Papanicolau staining was used.

Cytology diagnosis

The cytological diagnosis was classified as: Inadequate: smear with very few follicular cells (five or less per preparation) and no colloid. Benign or colloid: smear with a large amount of colloid, with few or no small-sized isolated follicular cells. Indeterminate nodules (FLUS/ AUS or FN/SFN): a- Follicular proliferation: smear with minimal or no colloid, with a haematic background and a major predominance of follicular cells measuring 2-3 times more than usual, arranged in follicular structures or leaves. b- Hürthle cell proliferation: follicular proliferation with Hürthle or oncocytic cells.

Suggestive of malignancy: this was subdivided into four groups: Papillary (cells with a metaplastic appearance or formation of papillae with connective axes, with typical nuclear alterations and occasionally the presence of Psammoma bodies). Follicular (follicular, aciniform or microfollicular cells, with large nuclear irregularities, and the presence of prominent nucleoli). Medullary (plasmocytoid appearance of the cells, generally isolated and intermingling with the amyloid). Undifferentiated (pleomorphic cells with an anaplastic appearance and multinucleated).

Statistical analysis

The thyroid FNAC results, grouped into suggestive of malignancy (positive result) vs. the rest of the diagnoses (negative result), were compared to the results of the final histological study of the excised specimen in order to calculate the values for the test to diagnose MNG-associated carcinoma: True positives (TP): positive result in the test for malignancy and confirmed in the histological study. False positives (FP): positive result in the test for malignancy but not confirmed in

the histological study. True negatives (TN): negative result in the test for malignancy, and no carcinoma in the histological study. False negatives (FN): negative result in the test for malignancy, but with a carcinoma in the histological study. Sensitivity (S): proportion of patients with associated carcinoma and a positive result in the test for malignancy, $S = TP / (TP + FN)$. Specificity (Sp): proportion of patients without associated carcinoma and with a negative result in the test for malignancy, $Sp = TN / (TN + FP)$. Positive predictive value (PPV): proportion of patients with a positive result and histological confirmation, $PPV = TP / (TP + FP)$.

RESULTS

Table (1): Diagnostic test results according to fine-needle aspiration cytology (N=20).

FNAC result	No.	Percent
Benign	13	65%
Intermediate	6	30%
Malignant	1	5%
Total	20	100%

The final histopathological diagnosis was benign lesion or tumor in 85% of the cases (N=17) and malignant in 15% of the cases (N=3). One patient had follicular thyroid carcinoma while two patients had malignant papillary thyroid tumor. The biopsy results are found in Table (2).

Table (2): Final histopathological test results according to biopsies (N=20).

Final diagnosis	Frequency	Percent
Benign lesion	17	85%
Papillary carcinoma	2	10%
Follicular carcinoma	1	5%
Total	20	100%

The results of thyroid FNAC revealed that 5% (n=1) of the patients had malignancies while histopathological results showed that the proportion of subjects with malignancies was 15% (n=3).

Out of the 13 cases identified to be benign lesion by thyroid FNAC, only 8% of the group subjects were found to be malignant follicular carcinoma by the final histopathological biopsy (N=1).

The 1 case that identified to be malignant by thyroid FNAC was confirmed to have papillary thyroid carcinoma by final histopathological biopsy.

Out of the 6 cases which were identified to be intermediate results by FNAC only 17 % (N=1) of the subjects was found to be papillary thyroid carcinoma by final histopathological biopsy and the rest of the intermediate group turned to be adenomatous goiter and colloid goiter (N=5).

Table (3) demonstrates that there was a good correlation between FNAC and final histopathology results.

Table (3): Correlation between fine-needle aspiration and final histopathology (N=20).

FNAC results diagnosis		Final histopathology results	
Results	Number	Benign	Malignant
Benign	13	12	1
intermediate	6	5	1
Malignant	1	0	1
Total	20	17	3

Final thyroid fine-needle aspiration result shown in Table (4).

Table (4): Final thyroid fine-needle aspiration results for the diagnosis of carcinoma in patients with multinodular goiter (N=20).

Result	Frequency
True positives	1 cases
False positives	0 cases
True negatives	17 cases
False negatives	2 cases
Sensitivity	33%
Specificity	100%
Positive predictive value	100%
Negative predictive value	89%
Diagnostic accuracy	90%

DISCUSSION

Thyroid Fine Needle Aspiration Cytology (FNAC) was introduced in Scandinavian countries in 1950s and became popular in the United States in 1970s and then worldwide in the 1980s. Today it remains the mainstay of diagnostic workup for thyroid pathologies (13).

Thyroid nodules are a common clinical finding and have a reported prevalence of 4–7% in the general population. The vast majority of these nodules are non-neoplastic lesions or benign neoplasms (14).

Thyroid FNAC is a safe and relatively simple test that is widely recognized as the critical, primary diagnostic procedure of first

choice for the evaluation of patients presenting with thyroid nodules. One of the major advantages is that FNAC can be done as an out-patient procedure (15).

As a triage tool, the FNAC biopsy can be used to distinguish thyroid nodules that might have a higher risk of malignancy (i.e., neoplasm), and would thus require surgical excision, from goitrous nodules or thyroiditis, which can be managed medically (16).

FNAC is relied upon to distinguish benign from neoplastic or malignant thyroid nodules and therefore has led to a dramatic decrease in thyroid surgeries. Nevertheless, Fine needle Aspiration has some limitations like specimen inadequacy and sampling techniques. Cytopathologist should be aware of these potential limitations and pitfalls of FNAC interpretation (17).

Fine needle aspiration biopsy has been proposed as the most important tool in the preoperative assessment of thyroid nodules. But, the efficiency of this method is highly dependent on the expertise of the operator as well as the pathologist, which leads to significant diversity about its sensitivity and specificity. The reported sensitivity and specificity of FNAC in previous studies ranged between 57% to 98% for sensitivity and 72% to 100% for specificity (18).

Various studies suggested that the sensitivity will improve if the procedure and its interpretation are performed by experienced practitioners (19).

It has been thought that the risk of cancer in a multinodular goiter is much less than that in a solitary nodule. The incidence of malignancy in multinodular goiter ranges from 1% to 10% (20).

However, recent literature indicates that if a nodule in a multinodular goitre has grown steadily, become distinctly dominant or changed in consistency, its risk of malignancy is the same as that of a solitary nodule (21).

Indeed, it has been shown that approximately 23% of single nodules are dominant in the context of a multinodular goiter. Conversely, some other reports revealed no increased risk of malignancy for multinodular goiters (MNG) (22).

FNAC as a diagnostic method in the management of MNG differs from that

performed in a solitary nodule and has certain peculiarities:

The first is when deciding which nodules are to be punctured. Several authors claim that it is not practical to puncture all the palpable nodules when the clinical suspicion of malignancy is low and propose puncture of one or two of the more prominent thyroid nodules of each thyroid lobe and those with suspected malignancy⁽²³⁾.

We again demonstrate that puncturing only the prominent nodule is more predictive for cancer rather than puncturing all palpable nodules; these results were also replicated by **Rios et al.**⁽⁶⁾ studies. No other factors may favor diagnosis of malignancy by FNAC like size or multifocality.

The second problem lies in the results, where there are two limitations, which are accentuated in MNG⁽¹⁶⁾.

The first limitation is nondiagnostic FNAC (0–25%), which implies inadequate material for diagnosis and has been correlated with the technique being performed correctly and the cytopathologist's experience⁽¹²⁾.

In our case, we excluded any nondiagnostic cytology from our research.

the major limitation of this technique is Suspicious or indeterminate FNAC (10–30%), suggesting follicular or Hürthle proliferation, as between 10% and 50% show malignancy, whereas a final diagnosis can only be established by histological criteria⁽²⁴⁾.

It must be remembered that a cytopathologist's experience is fundamental; there are studies that show that a review of FNAC results in a centre by another pathologist with experience implies a change in diagnosis of around 10%, several of them of therapeutic importance⁽²⁵⁾.

The main problem among the clinical features is false negatives, as it implies the presence of undetected carcinomas. Therefore, even if a puncture is negative, surgery must be indicated if there are clinical risk factors. As a general rule, the rate of malignancy in colloid FNAC ranges from 5% to 10%⁽²⁶⁾.

Tollin et al.⁽²⁷⁾ in a study on 61 MNGs proposed FNAC only in selected nodules concluded that FNAC under US guidance is a useful diagnostic modality in the

evaluation of thyroid nodules in selected patients with MNG.

It has been suggested that although FNAC is a useful test, our decision making should not be solely on the basis of its result and sometimes clinical and U/S criteria are preferred to cytologic data⁽²⁸⁾.

Moreover, MNGs are a common cause for lower predictive capacity and higher false negative results of FNAC, as reported by Cootough and Kaliszewski. Subsequently, they recommended total thyroidectomy for most of the cases with MNG in order to reduce the rate of reoperation despite a nonmalignant FNAC result⁽²⁹⁾.

Our series was a prospective study to evaluate the accuracy of FNAC in diagnosis of pathological type of dominant nodule in 20 patients with multinodular goiter who referred to the endocrine surgery unit at El-Demerdash Hospital in Ain Shams University from March 2017 to December 2017.

Our series is one of the few that analyze MNGs exclusively; others are **Rios et al.**⁽⁶⁾ and **Al-Yaarubi et al.**⁽¹⁶⁾

The FNAC results indicated malignancy in 1 patients (5%), benign in 13 patients (65%) and intermediate in 6 patients (35%).

The final histopathological diagnosis was malignancy in 3 of the patients (15%). one case had follicular thyroid carcinoma while two of the patients had malignant papillary thyroid tumor. Among the rest, 17patients (85%) had benign lesion or tumor.

The results of thyroid FNAC revealed that 5% of the patients had malignancies (N=1) while histopathological results showed that the proportion of subjects with malignancies was 15% (N=3).

Out of the 13 cases identified to be benign lesion by thyroid FNAC, only %8 of the group subjects were found to be malignant follicular carcinoma by biopsy(N=1).

Out of the 6 cases that were identified to be intermediate results by FNAC only 17 % of the subjects was found to be papillary thyroid carcinoma by final histopathology biopsy (N=1) and the rest of the intermediate group turned to be adenomatous goiter and colloid goiter (N=5).

The one case that was identified to have malignancy by thyroid FNAC was confirmed to have papillary thyroid carcinoma by final histopathology biopsy.

In our study, the FNAC sensitivity and specificity was 33% and 100%, respectively. The positive predictive value was 100%, while the negative predictive value was 89% and diagnostic accuracy 90%.

In our series we had 3 prominent nodules associated with cancer out of 20 patients while Ríos *et al.* reported 42 MNG associated with cancer in prominent nodules out of 423 patients with MNG⁽³⁰⁾.

Al-Yaarubi et al.⁽¹⁶⁾ reported the FNAC sensitivity and specificity was 16% and 97%, respectively and the positive predictive value was 53%, while the negative predictive value was 84%.

This coincides with the results reported by *Rios et al.*⁽⁶⁾ revealing a sensitivity of 17%, specificity of 96% and diagnostic accuracy of 88%, with a positive predictive value of 32% and negative predictive value of 88%.

Stojadinovic *et al.* reported up to 39% accuracy in the initial diagnosis when the results of FNAC was compared to histology or revised later by an expert cytologist⁽³⁰⁾.

CONCLUSION

Ultrasound guided FNAC is rapid, simple, safe, and cost-effective diagnostic modality in the investigation of the dominant nodule in patients with multinodular goiter. It can be used as an excellent first line method for investigating the nature of nodule. The primary diagnostic limit of FNAC is an inconclusive outcome, such as inadequate or indeterminate cytological samples.

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