A study of correlation of fine-needle aspiration cytology with postoperative histopathological examination in patients with either solitary thyroid nodule or multiple nodules

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Background Fine-needle aspiration cytology (FNAC) of the thyroid gland is now a well-established, first-line diagnostic test for the evaluation of thyroid nodules with the main purpose of confirming benign lesions and thereby, reducing unnecessary surgery. Different imaging techniques are now used for diagnosis of thyroid nodules like radionucleotide scanning and ultrasonography. 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.

Aim The aim of the work is to evaluate the correlation of preoperative FNAC with postoperative histopathological examination in patients with either solitary thyroid nodule and multiple nodules.

Patients and methods This prospective study was done between April 2016 and November 2017 on 100 patients presented to the General Surgical Department with either solitary or multiple thyroid nodule. This was done to assess the correlation between preoperative FNAC and postoperative histopathological examination.

Results Statistical analysis of our study showed sensitivity, specificity, accuracy, false-positive fraction, false-negative fraction, positive predictive value, and negative predictive value of FNAC to be 92, 81, 84, 36, 3.3, 63, and 96%, respectively.

Conclusion The FNAC is a sensitive, specific, and accurate initial diagnostic test for the preoperative evaluation of patients with thyroid swellings in our setting as well. The correlation of cytological and histopathological diagnoses is an important quality assurance method, as it allows cytopathologists to calculate their false-positive and false-negative results.

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Introduction

Fine-needle aspiration (FNA) biopsy of thyroid nodules is a minimally invasive and safe procedure that is usually performed on an outpatient basis. Either palpation or ultrasonography (US) may be used for guidance of FNA, but US has several advantages over palpation. Real-time US permits visualization of the needle within the lesion, thereby facilitating accurate biopsy of small nonpalpable nodules [1]. The value of fine-needle aspiration biopsy (FNAB) for diagnosis of thyroid pathologies has been established; however, in some specific situations, its reliability is debatable. This diagnostic tool is appropriate and valuable for the evaluation of single thyroid tumors but has shown less efficacy for that of multinodular thyroid glands. A false-negative FNAB result [when the appearance of cancer in a multinodular goiter (MNG) is missed] is a relatively rare occurrence in diagnosis of thyroid pathologies; however, it may occur in some cases of multinodularity of the thyroid gland. This result can arise when FNAB is performed on a targeted benign nodule, and a malignant process is recognized postoperatively in another nodule. Alternatively, certain technical limitations such as collection of nondiagnostic samples may cause a false-negative FNAB result. Currently, fine-needle aspiration cytology (FNAC) is one of the most popular and accurate techniques for presurgically evaluating thyroid nodules. It is possible to plan the extent of surgery and further treatment based on the results of this evaluation. The most valuable information that FNAC provides is whether a nodule has neoplastic potential [2]. Inadequate or improper sampling accounts for some false-negative errors. For example, nodules larger than 4 cm are too large to allow proper sampling from all areas, thereby increasing the likelihood of misdiagnosis. Finally, the cytopathologist should establish and observe criteria to exclude a diagnosis of malignancy [3]. Despite

enormous progress in clinical diagnostics in the past years, both the diagnosis and treatment of thyroid cancer remain challenging. An estimated diagnosis based on FNAB findings is not always concordant with that based on the final histopathological examination results. Additionally, incidental thyroid malignancy in a MNG is a very similar clinical situation that can occur and may interfere with diagnosis. One of the main difficulties of management of suspected malignancy in multiple thyroid tumors involves the decision of which nodule should be biopsied. There is no agreement among specialists regarding the selection of a nodule for biopsy, but sonographic characteristics that are predictive of malignancy have been described. They include a single nodule, a solid lesion, hypoechogenicity, and an irregular shape, edge, and size [4]. A variety of US characteristics are thought to differentiate benign from malignant thyroid nodule. These US features include echogenicity, internal echo pattern, margins, shape/dimension ratio, calcifications, acoustic phenomenon, compressibility, and vascularity. Although well-defined and smooth margins of a thyroid nodule may signify benignity, irregular or ill-defined lesions suggest malignancy. Although benign nodules are more likely to be entirely cystic in nature, many malignant lesions are solid and appear hypoechoic relative to adjacent thyroid tissue. Furthermore, thyroid nodules with a spongiform appearance comprising more than 50% multiple microcystic components are most likely benign. A thyroid nodule defined as being greater in its anteroposterior than its transverse dimension (i.e. taller greater than wider) has been described as more likely to be malignant than benign. Thyroid nodules with microcalcifications are more strongly associated with malignancy than those with coarse or no calcifications. Central vascularity is more likely to be characteristic of malignant thyroid nodules, whereas peripheral vascularity is associated with benign lesions. Apart from the index nodule, the presence of suspicious-appearing lymph nodes is also associated with thyroid malignancy. More recently, US compressibility or elastography was shown to distinguish between benign and malignant nodules, whereby significantly higher stiffness or less compressibility of the thyroid lesion was correlated highly with malignancy. This US technique, however, requires additional validation with prospective studies [3]. Some authors have suggested that the rate of detection of incidental thyroid carcinoma after surgery in patients with apparently benign MNG ranges from 3 to 16.6%. Additionally, they have noted that one-third of all patients who have received subtotal thyroidectomy for MNG require further surgical treatment [5]. Most often the first symptom of thyroid cancer is a nodule in the thyroid region of the neck. However, many adults have small nodules in their thyroids, but typically under 5% of these nodules are found to be cancerous. Sometimes, the first sign is an enlarged lymph node. Later symptoms that can be present are pain in the anterior region of the neck and changes in voice owing to an involvement of the recurrent laryngeal nerve. Thyroid cancer is usually found in a euthyroid patient, but symptoms of hyperthyroidism or hypothyroidism may be associated with a large or metastatic well-differentiated tumor. Thyroid nodules are of particular concern when they are found in those younger than 20 years. The presentation of benign nodules at this age is less likely, and thus the potential for malignancy is far greater [6]. Thyroid FNAB, particularly under US-FNA, is very safe. No serious complications such as tumor seeding, nerve damage, tissue trauma, or vascular injury have been reported. Needle puncture causes slight pain and some skin discoloration. Postaspiration hemorrhage within a cystic lesion can also occur [7]. Aspirates from normal glands often have scant thyroid follicular cells and colloid. Wet-fixed smears are usually prepared with a modified Papanicolaou stain, which shows nuclear details. Air-dried smears are often prepared with a Romanowsky stain. May–Grünwald–Giemsa is a modified Romanowsky staining procedure that is sometimes used in thyroid cytologic preparations. The conventional cytologic diagnosis includes four categories: benign (negative), suspicious (indeterminate), malignant (positive), or unsatisfactory (nondiagnostic). The new Bethesda classification has six categories, further expanding the indeterminate cytologies [8]. Cytological diagnosis of thyroid papillary carcinoma is not difficult when it shows a characteristic nuclear pattern and papillary structure of cell nests. In contrast, malignant follicular lesion is not easily differentiated from benign lesions cytologically. If follicular cells are seen with macrophages and degenerated cells in the colloid background, cytological diagnosis of nodular hyperplasia is entertained, and the lesion is usually considered as benign, although some might turn out to be malignant after resection. The term follicular neoplasm has been applied to the presence of abundant follicular epithelial cells in sheets, in microfollicles or a trabecular pattern with scanty or no colloid. The important issue is the concern that such a lesion might be follicular carcinoma. The definition of a follicular carcinoma is primarily based on histologic

evidence of capsular or vascular invasion extrathyroidal tissue invasion, or nodal or distant metastasis [9].

Aim

The aim of the work is to evaluate the correlation of preoperative FNAC with postoperative histopathological examination in patients with either solitary thyroid nodule and multiple nodules.

Patients and methods

This prospective randomized study was done between April 2016 and November 2017 on 100 patients presented to General Surgical Department with either solitary or multiple thyroid nodule, 50 patients presented to Al Zahraa University Hospital and 50 patients presented to Damanhour Medical National Institute. This study was done to assess the correlation between preoperative FNAC and postoperative histopathological examination.

Inclusion criteria

All patients presented with solitary or multiple thyroid nodules were included. Exclusion criteria were as follows: all cases of thyroiditis, all patients with comorbidities and unfit for surgery, all patients who refused surgery, and all patients with diffuse goiter with no solitary or multiple thyroid nodules.

All patients in the present study were subjected to the following:

(1) Complete history taking and full clinical examination.
(2) Laboratory investigations included the following:
    (a) Full blood count.
    (b) Blood urea and creatinine.
    (c) Serum liver enzymes such aspartate transaminase and alanine transaminase; fasting blood sugar; T3, T4, free T3, free T4, and thyroid-stimulating hormone estimation; and thyroglobulin, anti-thyroglobulin, and calcitonin when indicated.
(3) Imaging evaluation included the following:
    (a) Neck US:
        It is a simple, safe, and noninvasive imaging modality that employs a high-frequency sound wave with imaging for detection of multinodularity, determination of the size of the gland, and US nature of the nodule, guidance of FNA of very small lesions and exploration of the neck for enlarged lymph nodes.
    (b) Chest radiograph for retrosternal goiter and preoperative assessment.
    (c) Computed tomographic scan was used selectively in patients with massive, retrosternal, or clinically malignant goiter, or in suspected posterior extension of the nodules.
(4) ECG
(5) Histopathological examination:
    (a) Preoperative FNAC: the thyroid gland was palpated carefully, and the nodule(s) to be biopsied identified. The procedure was explained carefully to the patient, and all the patient's questions were answered completely. We informed our patients that local anesthetic is not used, that the biopsy takes several minutes, that three to six aspirations are made, and that we expect no serious complications, but there was slight pain similar to a venipuncture.
    (b) Histopathological examinations: FNAC results have been correlated with postoperative histopathological results.

Statistical analysis

The followings tests were used in statistical analysis:

(1) χ^2 test (χ^2, P: χ^2 and P values).
(2) Monte Carlo for χ^2 test (^{MC}P: P value).
(3) Fisher's exact for χ^2 test (^{FE}P: P value).
(4) Student's t test for comparing between the two groups (t, P: t and P values).

Statistical significance was set at P value less than or equal to 0.05.

Results

Patients' ages ranged from 15 to 79 years, with a mean of 45.36 (SD 14.85) years. Most patient ages were found in the fourth and fifth decades of life (55%). In this study, 80 (80%) patients were females and 20 (20%) patients were males, with female to male ratio of 4 : 1. Neck US was done for all patients, which revealed 18 (18%) cases with solitary thyroid nodule and 82 (82%) cases with MNG. Computed tomographic scan was done in 31 (31%) patients. Aspirates were obtained from 100 patients. The procedure was very well tolerated by the patients, with minimal complications. Only seven (7%) patients developed local hematoma, which was discovered during the operation. The aspirate was unsatisfactory in only three (3%) patients; 61 (61%)

aspirates showed benign lesions, 14 (14%) were suspicious, and 22 (22%) were malignant. Final postoperative histopathological examination revealed 75 (75%) benign cases: 13 (13%) colloid nodules, six (6%) adenomas, 22 (22%) simple MNG, 29 (29%) toxic MNG, and five (5%) cysts. A total of 25 (25%) cases were malignant: 15 (15%) were papillary carcinoma, five (5%) follicular carcinoma, two (2%) medullary carcinoma and three (3%) anaplastic carcinoma. Overall, 97 (97%) cases were treated by surgery: 15 (15.5%) hemithyroidectomies and 82 (84.5%) total thyroidectomies. Neck dissection was performed in seven (7.2%) malignant cases, and three (3%) cases received no surgical treatment (cases with anaplastic carcinoma). Of 25 patients with thyroid cancer on histopathology results, 21 cases underwent total thyroidectomy; one case of follicular carcinoma underwent hemithyroidectomy, which further required completion thyroidectomy; and three cases with anaplastic carcinoma received no surgical treatment. Adjuvant therapy was received in 17 (17%) cases, where 15 patients received radioactive iodine, one patient received external irradiation, and one patient received chemoirradiation (Tables 1–3).

Discussion

The current study showed that 76 (76%) patients presented with a neck swelling, one (1%) patient with dysphagia and dyspnea, one (1%) patient presented with pain, one (1%) patient with voice change, and 21 (21%) patients presented with toxic manifestations. Local examination revealed 73 (73%) patients had firm nodule, whereas 19 (19%) were hard and the remaining eight (8%) nodules were cystic. Local examination revealed that 95 (95%) cases of swelling moved with deglutition, whereas five (5%) swelling were fixed to other neck structures, which proved to be malignant on histopathological examination. Enlarged cervical lymph nodes were found in seven (7%) cases clinically and by US, whereas other 93 (93%) cases were normal. Fazal *et al.* [10] had reported the main complaints of the patients were neck swelling (100%), vocal cord palsy (6.09%), breathing difficulty (4.87%), and dysphagia. Kaplan [11] reported that differentiated thyroid carcinoma is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. Approximately 50% of the malignant nodules are discovered during a routine physical examination, on imaging studies, or during surgery for benign disease. The other 50% are usually noticed first by the patient, usually as asymptomatic nodules [11]. Fifteen (15%) patients in our series had papillary carcinoma, follicular carcinoma was the second common as it was found in five (5%) patients, three (3%) patients had anaplastic carcinoma, whereas two (2%) patients had medullary carcinoma. In the study done by Michael *et al.* [12], of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, 80% had papillary carcinoma, 11% had follicular carcinoma, 3% had Hürthle cell carcinoma, 4% had medullary carcinoma, and 2% had anaplastic thyroid carcinoma. The diagnostic value of FNAC in our study was as follows: 23 (23.7%) cases were true positive, whereas 59 (60.8%) cases were true negative. In our study, false-positive cases were 13 (13.4%); 13 cases were suspicious on FNAC, whereas on histopathology, they turned out to be benign thyroid diseases, representing three cases of colloid nodule, three cases of follicular adenoma, and seven cases of simple nodular goiter. In this study, two (2.1%) cases were false negative, which were benign thyroid diseases by FNAC, but were diagnosed as follicular carcinoma on histopathology. In the series by Bagga and Mahajan [13], the FNAC results were compared with the corresponding histological diagnoses. The FNAC results were interpreted as inadequate in four (1.6%), benign in 228 (90.5%), suspicious in 17 (6.7%), and malignant in three (1.2%). The histopathological findings of 32 cases that underwent surgery were benign in 26 and malignant in six. The malignant cases comprised papillary carcinoma (50%), follicular carcinoma (33.3%), and medullary carcinoma (16.7%). We identified no false-positive cases. There was one false-negative case, given as cystic colloid goiter on cytology, which was finally diagnosed as papillary carcinoma on histopathology. Analysis of the results yielded a sensitivity of 66%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 96%, with a diagnostic accuracy of 96.2% [13]. Statistical analysis of our study showed sensitivity, specificity, accuracy, false-positive fraction, false-negative fraction, positive predictive value, and

Table 1 Reliability of fine-needle aspiration cytology in the diagnosis of thyroid malignancy (*N*=100)

	FNAC [*n* (%)]				χ^2	^{MC}P
	Benign (*N*=61)	Suspicious (*N*=14)	Malignant (*N*=22)	Unsatisfactory (*N*=3)		
Benign	59 (96.7)	13 (92.9)	0 (0.0)	3 (100.0)	80.562*	<0.001*
Malignant	2 (3.3)	1 (7.1)	22 (100.0)	0 (0.0)		

FNAC, fine-needle aspiration cytology; MC, Monte Carlo. *$P \leq 0.05$ (Significant).

Table 2 Relation between fine-needle aspiration cytology and histopathology results (*N*=100)

Histopathology results	FNAC [*n* (%)]				χ^2	^{MC}P
	Benign (*N*=61)	Suspicious (*N*=14)	Malignant (*N*=22)	Unsatisfactory (*N*=3)		
Colloid nodule	9 (14.8)	3 (21.4)	0 (0.0)	1 (33.3)	6.547	0.072
Follicular adenoma	2 (3.3)	3 (21.4)	0 (0.0)	1 (33.3)	9.560*	0.018*
Simple multinodular goiter	15 (24.6)	7 (50.0)	0 (0.0)	0 (0.0)	14.077*	0.001*
Toxic multinodular goiter	29 (47.5)	0 (0.0)	0 (0.0)	0 (0.0)	28.606*	<0.001*
Cyst	4 (6.6)	0 (0.0)	0 (0.0)	1 (33.3)	5.039	0.150
Papillary carcinoma	0 (0.0)	0 (0.0)	15 (68.2)	0 (0.0)	50.384*	<0.001*
Follicular carcinoma	2 (3.3)	1 (7.1)	2 (9.1)	0 (0.0)	2.380	0.418
Medullary carcinoma	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	6.078	0.124
Anaplastic carcinoma	0 (0.0)	0 (0.0)	3 (13.6)	0 (0.0)	8.071*	0.025*

FNAC, fine-needle aspiration cytology; MC, Monte Carlo. $P>0.05$ (non-significant). *$P\leq0.05$ (Significant).

Table 3 Relation between type of operation and histopathology results (*N*=97)

Histopathology results	Hemithyroidectomy (*N*=15) [*n* (%)]	Total thyroidectomy (*N*=82) [*n* (%)]	χ^2	^{FE}P
Colloid nodule	5 (33.3)	8 (9.8)	6.074*	0.028*
Follicular adenoma	6 (40.0)	0 (0.0)	34.963*	<0.001*
Simple multinodular goiter	0 (0.0)	22 (26.8)	5.205*	0.020*
Toxic multinodular goiter	0 (0.0)	29 (35.4)	7.567*	0.004*
Cyst	3 (20.0)	2 (2.4)	7.999*	0.025*
Papillary carcinoma	0 (0.0)	15 (18.3)	3.246	0.117
Follicular carcinoma	1 (6.7)	4 (4.9)	0.083	0.577
Medullary carcinoma	0 (0.0)	2 (2.4)	0.374	1.000
Anaplastic carcinoma	0 (0.0)	0 (0.0)	–	–

FE, Fisher's exact test. $P>0.05$ (non-significant). *$P\leq0.05$ (Significant).

negative predictive value of FNAC to be 92, 81, 84, 36, 3.3, 63, and 96%, respectively. Statistical analysis of other study data showed the diagnostic accuracy of FNAC to be 98.48%. FNA showed a sensitivity of 97% and a specificity of 100%. The negative and positive predictive values were 100 and 96%, respectively [14]. Another study on FNAC achieved a sensitivity of 92.8%, specificity of 94.2%, positive predictive value of 94.9%, negative predictive value of 91.8%, and a total accuracy of 93.6% [15].

Conclusion and recommendation

The FNAC is a sensitive, specific, and accurate initial diagnostic test for the preoperative evaluation of patients with thyroid swellings. Avoiding false-positive and false-negative results requires determination of the adequacy of an aspirate, cellular atypia, application, and interpretation of immunostains. Larger nodules are more likely to yield false-negative results. To improve sampling, aspirates should be obtained from multiple sites of the nodule rather than repeatedly from a single spot. The absence of malignant cells in an otherwise acellular specimen does not exclude malignancy. It is good practice to biopsy all accessible nodules in a multinodular gland. In patients with multiple nodules, US-FNA is the method of choice for selecting nodules for FNA when US features are suspicious .We recommend FNAC as a routine initial modality in the evaluation of patients with solitary and multiple thyroid nodule.

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Conflicts of interest

There are no conflicts of interest.

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