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ROLE OF CLINICAL ASSESSMENT, INVESTIGATION, RADIOLOGY AND FNAC IN PREOPERATIVE DIAGNOSIS OF THYROID CARCINOMA

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ABSTRACT

Background: Goiter is defined as an enlargement of the thyroid gland and it had been recognized since 2700B.C. Thyroid cancer is responsible for six deaths per million persons annually. Most patients present with a palpable swelling in the neck. The finding of a clinically solitary non toxic thyroid nodule has usually being a strong indication for surgery because it is considered to be a highly suspicious sign of carcinoma.
Aim of study: To evaluate the role and accuracy of history taking, physical examination and FNAC in the pre-operative diagnosis of thyroid cancer.
Methods: This prospective study was conducted at Al Yarmouk Teaching Hospital over a period of twenty three months involving 87 cases with thyroid enlargement with features suggesting thyroid cancer. The diagnosis of thyroid cancer was made on history, physical examination, and FNAC finding. Data was studied, categorized in tables according to history, examination, and FNAC findings, then assessed and analyzed. The details of histopathological results where recorded and compared to the initial FNAC results.
Results: A total of 87 patients with mean age of 41.7±7.4 years were enrolled in this study, the malignant nodule of more than 2 cm was significantly differed from benign one as well as the percentage of irregular edge of malignant tumor was significantly higher than those of benign one. Our study revealed a significant association between FNAC finding and histopathological finding (p=0.01), where the result showed 65 (84.4%) out of 68 (78.2%) of patients who were labeled as malignant by FNAC was also labeled as malignant by histopathological examination (sensitivity of FNAC = 84.4%) and 7 (70.0%) out of 19 (21.8%) who were labeled as benign by FNAC were also labeled as benign by histopathological results (specificity of FNAC = 70%).
Conclusion: In our study, history and examination are the first measure in the evaluation of solitary thyroid nodule. The evaluation of thyroid FNAC samples are highly correlated with the results of histopathological diagnosis. FNA biopsy is the preferred diagnostic test in all patients with thyroid nodules. It is safe, simple, reliable, and cost-effective mean for differentiation between malignant and benign nodules.

INTRODUCTION

Goiter is defined as an enlargement of the thyroid gland, it had been recognized since 2700 B.C. Even though, the thyroid gland was not documented as such until the Renaissance period. The term thyroid gland is attributed to Thomas warton (Geeta Lal, 2015). The first account of thyroid surgery for the treatment of goiters were given by Roger Frugardy in 1170. In response to failure of medical treatment, two setons were inserted at right angles into the goiter and tightened twice daily until the goiter separated (Geeta Lal, 2015).

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The normal thyroid gland weighs 20–25 g. The functioning unit is the lobule supplied by a single arteriole and consisting of 24–40 follicles lined with cuboidal epithelium. The follicle contains colloid in which thyroglobulin is stored (Krukowski, 2013). The arterial supply is rich, and extensive anastomoses occur between the main thyroid arteries and branches of the tracheal and oesophageal arteries. There is an extensive lymphatic network within the gland. Although some lymph channels pass directly to the deep cervical nodes, the subcapsular plexus drains principally to the central compartment juxtathyroid nodes – 'Delphian' (level 6) – ,paratracheal nodes (level 7) and nodes on the superior and inferior thyroid veins, and from there to the deep cervical (levels 2, 3, 4 and 5) and mediastinal groups of nodes.[(2)]

THYROID cancer accounts for less than1% of all malignancies (2% of women and 0.5% of men) and is the most rapidly increasing cancer in women. Thyroid cancer is responsible for six deaths per million persons annually. Most patients present with a palpable swelling in the neck, which initiates assessment through a combination of history, physical examination, and FNAC (Akerstrom, 2007). The prevalence of thyroid nodules which are solitary at palpation in general population is high , report rates ranges from (4%-7%), being lowest in males and highest in middle aged women (Mazzaferri, 2005). The finding of a clinically solitary non toxic thyroid nodule has usually being strong indication for surgery because it is considered to be a highly suspicious sign of carcinoma. The reported incidence of cancer in these cases has been very variable, ranging between 3% and 36%. In most instances, too many operations are perforemed in order to find a few cancers (Vander and Psarras, 2011). The management of thyroid nodules has changed over the past two decades The traditional approach of removing all thyroid nodules has given way to more cost effective and accurate diagnostic testing that allows to treat surgically those nodules likely to be malignant and treat conservatively those that are benign (Psarras, 2011). Since the solitary nodule is the most common sign of thyroid carcinoma, there is a need for inexpensive, simple and safe methods to identify correctly those nodules that have to be managed surgically because of malignancy risk (Bhaijee, 2011).

Since the clinical features alone are not deciding, various forms of investigations have been used to solve this problem but still each had its own limitations (Bhaijee, 2011). The ideal investigation for solitary thyroid nodule should differentiate between benign and malignant nodules, so that the percentage of thyroid operations for cancer increase, and unnecessary surgery for benign nodules is avoided. Thyroid cancer may be slowly growing, where as a benign nodule may rapidly enlarge and become painful because of hemorrhage (American Thyroid Association, 2009). Local obstructive symptoms are non-specific and may be associated with benign as well as malignant disease. Immobility of nodule, local adenopathy or evidence of tracheal or recurrent laryngeal nerve invasion are all important indicators for malignancy (American Thyroid Association, 2009). History taking, physical examination, and FNAC, are the main stay in the evaluation of thyroid nodule and goiter (Nikiforov, 2011). Imaging studies are of value in confirming the diagnosis of malignancy, the extent of the disease, involvement of local organs or tissues, possible distance metastasis, preoperative staging and as a guide for further management (Nikiforov, 2011). Cancer of the thyroid gland accounts for 1% of all cancers and is responsible for 0.5% of cancer-related deaths. Early diagnosis still maintains its importance for higher life expectancy due to the low malignant potential of thyroid nodules, and slow progressing characteristics of thyroid gland cancers, no single diagnostic methods used for the definitive diagnosis of thyroid cancers, such as radiographs, U/S, scintigraphy and suppression therapy, is effective enough to make a benign/ malignant differentiation alone (Muratli *et al*., 2014). Epidemiological studies have shown that thyroid nodules can be detected by palpation in 5% of cases and detection with high-resolution ultrasound (U/S) ranged between 19 and 67 % (Cooper, 2009). In this study, the effectiveness of FNAC was evaluated through the identification of the correlation between the cytological diagnoses of thyroid nodules by FNAC and the postoperative histopathologic diagnoses. FNAC is easy to apply, has a low complication rates and high diagnostic value and is a cost-effective test used in the diagnosis of thyroid nodules (Gharib, 2008). The use of FNAC resulted in a decrease in the number of patients who underwent surgical treatment by 25-50%, while increasing the percentage of malignant results in the operated group of patients (Hadi and Razouki, 2012). Currently, FNAC is the preferred diagnostic method for the initial stage of evaluation of thyroid nodules (Nikiforova, 2008). Ultrasounography is the imaging modality most commonly used to evaluate thyroid disease. The usefulness of U/S to distinguish between the malignant and benign thyroid disease is limited, even cysts seen in ultrasound could be complex and these may potentially harbor malignancy (Cibas, 2005). Microcalcification noted on ultrasound is associated with malignancy. Radioiodine imaging can help in determining the functional status of a nodule but carcinoma can not be excluded on the bases of radioiodine scan. In select situations like cold nodule, such scans can act as a diagnostic adjuvant. CT scanning and MRI can be used to evaluate soft tissue extension of large or suspicious masses of the neck, trachea or esophagus and to assess metastasis to the cervical lymph nodes . They have no role in the routine management of solitary thyroid nodules (Bagga, 2010).

Aim of study

To evaluate the role and accuracy of history taking, physical examination and FNAC in the preoperative diagnosis of CA thyroid.

Patients and Methods

This prospective study was conducted at Al Yarmouk Teaching Hospital, in department of surgery over a period of twenty three months (from 1st of January 2014 to 1st of December 2015) involving 87 cases with thyroid enlargement with features (history, examination and FNAC) suggesting thyroid cancer. Regarding FNAC and histopathological results, most of them were done in Al-Yarmouk hospital, the rest done out side with different number of persons and degrees. The diagnosis of thyroid cancer was made on history, examination, risk factors (male gender, size and diameter of nodule, fixation, L.N, history of radiation and positive family history). In addition to history, examination, the diagnosis of CA thyroid had been based on FNAC finding. Data was collected initially on admission regarding age, gender, family history, symptoms and sign of presentation and if there is history of radiation exposure. A question naire was prepared. Patients were followed up during the period of the study about the investigation, and preparation to operation and post operative period. Data was studied, categorized in tables to find any relations between data obtained and the incidence of thyroid cancer. The Statistical Package for Social Science (SPSS) version 20 was used for data entry and analysis. Frequency and percentage were used to describe the results and Suitable statistical tests were used accordingly. Chi-Square test and Fisher's Exact Probability test were used to test association between dependent and independent variables. P value < 0.05 was considered significant.

RESULTS

A total of 87 patients with mean age of 41.7±7.4 years were enrolled in this study, (42±7sd) for patient for with malignant

tumor and (43±11sd) years for (benign=0.6), the results showed that the distribution of patients according to final histopathological finding with regards to age category, gender of the patients, history of radiation exposure and family history of thyroid cancer was of no difference significantly for all tested parameters ($p \geq 0.05$) as displayed in Table.1.2.3.4.

Table 1. Histopathological findings according to age for studied group

Category		Diagnosis by histopathology				P-value
		Malignant		Benign		
		NO.	%	NO	%	
Age	<30	4	5.2%	1	10.0%	0.5
	30-39	21	27.3%	4	40.0%	
	40-49	45	58.4%	3	30.0%	
	50-59	4	5.2%	1	10.0%	
	>60	3	3.9%	1	10.0%	

Table 2. Histopathological findings according to gender for studied group

Category		Diagnosis by histopathology				P-value
		Malignant		Benign		
		NO.	%	NO	%	
Gender	Female	58	75.3%	8	80.0%	0.7
	Male	19	24.7%	2	20.0%	

Table 3. Histopathological findings according to radiation history for studied group

Category		Diagnosis by histopathology				P-value
		Malignant		Benign		
		NO.	%	NO	%	
Radiation history	Negative	62	80.5%	6	60.0%	0.9
	Positive	15	19.5%	4	40.0%	

Table 4. Histopathological findings according to family history for studied group

Category		Diagnosis by histopathology				P-value
		Malignant		Benign		
		NO.	%	NO	%	
Family history of CA thyroid	Negative	52	67.5%	9	90.0%	0.4
	Positive	25	32.5%	1	10.0%	

Our findings reported that there was no significant difference regarding the clinical presentation between patients with malignant tumor and those with benign one even the patients with malignant tumor have had higher percentage of positive findings but this is does not reach the significant level ($p \geq 0.05$ for all) as displayed in Table 5.

Table 5. Clinical presentation of patients according to Tumor type

clinical presentation		Diagnosis by histopathology				P-value
		Malignant		Benign		
		NO.	%	NO.	%	
Dyspnea	Yes	24	31.2%	3	30%	0.9
	No	53	68.9%	7	70%	
Dysphagia	Yes	7	9.9%	5	50%	0.05
	No	70	90.9%	5	50%	
Weight loss	Yes	21	27.3%	2	20%	0.05
	No	56	72.7%	8	80%	
Hoarseness	Yes	1	1.3%	0	0.0%	0.7
	No	76	98%	10	100%	

The results demonstrated that the patients with malignant tumor were not different significantly from those with benign tumor with regards to number of nodule, nodule statues free or fixed, consistency, retrosternal extension, skin changes, nature of the surface and lymph node involvement($p \geq 0.05$). The results showed that the malignant nodule of more than 2 cm was significantly different from benign one, as well as the percentage of irregular edge of malignant tumor was significantly higher than those of benign one($p=0.03$ for both as displayed in Table 6. The results revealed a significant association between FNA finding and histopathological finding ($p=0.01$), where the results showed 65 (84.4%) out of 68 (78.2%) patients who were labeled as malignant by FNA were also labelled as malignant by histopathological examination (sensitivity of FNA=84.4%) and 7 (70.0%) out of 19 (21,8%) who were labeled as bengin by FNA results were also labeled benign by histopathological results (specificity of FNA=70%) as seen in Table. 7,8.

DISCUSSION

Cooper DS.*et al* reported that the malignancy rates increase in older patients (Bagga, 2010; Yassa, 2007 and Melillo, 2010). The mean age of our patients was 41.7 years±7.4 and this finding is slightly lower to what is found by Muratli. *et al*, 2014(51 years). (Muratli *et al*., 2014), and higher than Garg.S *et al*, 2105. Muratli *et al* reported that the higher mean of age was because of a large sample with varied age groups. Although there are conflicting reports about gender as a risk factor for thyroid cancer, in our study we found that the rate of malignancy was higher in female patients compared to male patients and we think that the reason here is a high frequency of female patients with goiter who were enrolled in our study. In addition we found that the percentage of patients with malignant tumor who have had a family history of thyroid malignancy and a history of exposure to radiation were higher than those with benign tumor even this difference wasnot significant. In North America, Schneider. *et al* showed that thyroid nodules can be detected with U/S in 67% of population (Schneider, 2005). Our finding reported that there was no significant difference with regards to sex of the patients and the female/male ratio in malignant nodule was about 3:1 and this finding similar to what was reported by Dal Maso (2009). It is reported that the increased risk of malignancy in patient with a familial history, might be due to both a hereditary effect, and the sharing of a causative environmental factor.

In addition radiation, iodine deficiency, and some genetic syndromes are widely accepted to be correlated with the risk of thyroid cancer, but their clinical implication in the general population has been limited (Schneider, 2005; Dal Maso, 2009 and Moore, 2006). Triponez. *et al* reported that the probability of thyroid cancer increased with an increasing number of affected first-degree family members and the familial tendency was most clearly demonstrated among sisters (Triponez, 2006; Hemminki, 2005). With regards to nodule number, Rago *et al* (Rago, 2010; Barroeta, 2006), suggested that a solitary nodule is more likely to be malignant, but other report have suggested that the number of nodules is not correlated with malignancy (Bouhabel, 2012). Frates *et al*. (Frates, 2006), reported that the likelihood of malignancy per person was independent of multiplicity, but that the rate of malignancy is not closely related with the number of nodules in multinodular disease. We found that all of the clinical features apart from weight lose with malignant tumor, sex difference and U/S findings were not-significantly different between patients with benign and malignant nodules.

Table 6. Clinical examination finding according to tumor type

Clinical examination		Diagnosis by histopathology				P-value
		Malignant		Benign		
		NO.	%	NO.	%	
Number of nodule	Solitary nodule	60	77.9%	9	90%	
	Multinodular	17	22.1%	1	10%	
Nodule fix/free	Fixed	7	9.1%	0	0.0%	0.3
	Free	70	90.9%	10	100%	
Nodule consistency	Hard	13	16.9%	1	10%	0.5
	Soft	64	83.1%	9	90%	
Nodule size	<2 cm	53	68.8%	8	80%	0.03
	>2 cm	24	31.2%	2	20%	
Skin change	Yes	1	1.3%	0	0.0%	0.7
	No	76	98.7%	10	100%	
Retrosternal extension	Yes	25	32.5%	3	30%	0.1
	No	52	67.5%	7	70%	
Surface	Smooth	26	33.8%	6	60%	0.1
	Rough	51	66.2%	4	40%	
Nodule edge	Regular	52	67.5%	10	100%	0.03
	Irregular	25	32.5%	0	0.0%	
Lymph node involvement	Yes	3	3.9%	0	0.0%	0.5
	No	74	96.1%	10	100%	

Table 7. Relationships of FNAC and histopathological findings

FNA finding		Histopathological finding		Total	P-value
		Positive (malignant)	Negative (benign)		
Positive (malignant)	NO.	65	3	68	0.01
	% within Histopathological finding	95.6%	44.4%	100%	
		TP	FP		
Nagative(benign)	NO.	12	7	19	
	% within Histopathological finding	15.6%	70.0%	21.8%	
		FN	TN		
Total	NO.	77	10	87	
	% within Histopathological finding	100.0%	100.0%	100.0%	

Table 8. Accuracy of FNA findings

FNA	sensitivity	specificity	PPV	NPV	accuracy
	95.6	70	95.5	36	76.2

We considered the higher numbers of malignant cytology results in female patients were due to the higher frequency of females patients with goiter. The sensitivity and specificity ratios for FNA range between 65% - 98% for sensitivity and 73%-100% for specificity as reported by Bagga *et al*. (Bagga, 2010; Pandey, 2012 and Haberal, 2009). We found that the sensitivity of FNAC was 84.4% and specificity was 70% and the most accepted explanation for this wide range of difference in sensitivity and specificity of FNA that was reported in different published series might belong to the way that the suspicious lesion was categorized in different researches, in addition to difference in experience of cytopathologists.

We found the rate of false-negative as 15.6% and the rate of false-positive as 30%, while the rate reported by Bagga *et al*. showed a false-negative rates was between 1% and 7% and false-positive rates between 1% and 11.6 % (Bagga, 2010; Esmaili, 2012 and Melillo, 2010). Muratli *et al* showed that among the factors that reduce the efficiency of FNAC are inadequate sampling, inexperience of the cytopathologists and natural difficulties of differentiation of benign and malignant follicular lesions (Muratli, 2014; Ali *et al*., 2011 and Borget, 2008), recorded that from the factors that might reduce the efficiency of FNA test was inadequate sampling which often results from sclerotic, calcified nodules or nodules with cystic degeneration in larger areas and U/S guided sampling reduces the non- diagnostic test rates in such conditions.

It is estimated that 15–30 % of FNA samples yield indeterminate results, of which 70–85 % are diagnosed to be benign after thyroidectomy (Aspinall, 2013; Sosa, 2013). Two major challenges facing clinicians are; how to distinguish malignant from benign nodules and how to identify those thyroid malignancies that are aggressive. Fine needle aspiration (FNA) cytology represents the primary preoperative diagnostic tool for the evaluation of thyroid nodules, but it is inconclusive in up to 30% of patient's. In particular, follicular carcinoma is difficult to distinguish from benign follicular lesions by cytology (Jee, 2016; Jing, 2008). Various diagnostic terminologies, including "indeterminate", atypical", and "suspicious for malignancy," were used to describe these challenging cases. Until recently there were no uniform criteria for the various diagnostic categories in thyroid cytopathology. This resulted in diagnostic inconsistencies among different laboratories and difficulty in communicating the implications of thyroid fine-needle aspiration (FNA) results both to clinicians (endocrinologists and endocrine surgeons) and laboratory doctors (pathologists and radiologists), (Misiakos *et al*., 2016).

Conclusion

- History taking and physical examination are the initial measure in the evaluation of solitary thyroid nodule.

- The evaluation of thyroid FNAC samples is highly correlated with the results of histopathological diagnosis.
- FNA biopsy is the preferred diagnostic test in all patients with thyroid nodules. It is a safe, simple, reliable, and cost-effective mean for differentiation between malignant and benign nodules.

Recommendation

- Early evaluation of any suspicious thyroid nodule by history, examination and FNAC.
- Thyroid clinic establishment.

Abbreviations

CA	Carcinoma
FNAC	Fine needle aspiration cytology
U/S	Ultrasound
CT scan	Computed tomography
MRI	Magnetic Resonance Imaging
L.N	Lymph node
sd	Standard deviation

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