Triple Assessment of Breast Lumps
The Efficacy for the Detection of Breast Cancer Disease in Iraqi Females

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ABSTRACT

Background: Breast is the most site-specific cancer in women; it is the leading cause of death from cancer in women aged 20-59 years. It account for 26% of all newly diagnosed cancer in women and responsible for 15% of cancer related death in women.
Objective: To evaluate the efficiency of triple assessment {Clinical examination (C/E), imaging technique and Fine needle aspiration cytology (FNAC)} of breast lumps for the detection of breast cancer disease in Iraqi females presenting to the breast clinic and apply the results obtained in the proper management of breast pathology.
Methods: A case series study carried out at Al-Yarmouk Teaching Hospital during the period from 1st July 2011 to 31st December 2012, in which a selected sample of 156 patients was studied. The study includes female patients that attend the breast clinic in Al-Yarmouk Teaching Hospital and were followed to have the last conclusive results of histopathology.
Result: There were 117 (75%) benign lesions and 39 (25%) malignant lesions. The sensitivity of C/E was 79.5% and specificity 89.7%, and that For U/S were 89.7% and 96.6%, and for Mammography were 87.2% and 95.7% respectively; while that of FNAC were 92.3% and 98.3% respectively and the sensitivity of triple assessment was 94.9% and specificity was 100%.
Conclusion: The triple assessment is a sensitive, specific, accurate, simple, easy, fast, minimally invasive and a low-cost assessment system that can be applied in the initial breast clinic visit reaching the diagnosis in comparison to the final diagnosis with the histopathology.
Keywords: Breast lump, Breast cancer, Triple assessment.

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Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20 to 59 years[1,2]. It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer-related deaths in women [2]. It was predicted that approximately 182,460 invasive breast cancers would be diagnosed in women in the United States in 2008 and that 40,480 would die from breast cancer[3]. Breast cancer was the leading cause of cancer-related mortality in women until 1987, when it was surpassed by lung cancer. More than a million cases of breast cancer are diagnosed worldwide each year[4].

Most of the breast masses are benign. The overall incidence of breast cancer has been rising because of increases in the average life-span and lifestyle changes that increase risk for breast cancer[5].

In any patient who presents with a breast lump or other symptoms suspicious of carcinoma, the diagnosis should be made by a combination of clinical assessment, radiological imaging and a tissue sample taken for either cytological or histological analysis, the so called triple assessment. It was initially described in 1975, by Haagensen, which is the evaluation of palpable breast masses by physical examination, imaging (mammography >35 years, U/S <35 years) and fine-needle aspiration. The positive predictive value (PPV) of this combination should exceed 99.9%[6]. An efficient and accurate evaluation can maximize cancer

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detection and minimize unnecessary testing and procedures[7].

The triple test is the combination of results from clinical breast examination, imaging, and tissue sampling. When the three assessments are performed adequately and produce concordant results, the triple test diagnostic accuracy approaches 100 percent. Discordant results or results that cannot be evaluated may indicate the need for excisional biopsy.

The Triple Test Score (TTS) was developed to help physicians interpret discordant triple test results. A three-point scale is used to score each component of the triple test (1 = benign, 2 = suspicious and 3= malignant). A TTS of 3 or 4 is consistent with a benign lesion; a TTS of 6 or more indicates possible malignancy that may require surgical intervention. Excisional biopsy is recommended in patients with a TTS of 5 to obtain a definitive diagnosis[8].

Methods

This study is a retrospective case series study carried out at Al-Yarmouk Teaching Hospital during the period from 1st of July 2011 to 31st of December 2012, in which a selected sample of 156 patients was studied. The study includes female patients that attend the breast clinic in our hospital and were followed until the conclusive histopathology results were obtained.

Data collected includes demographic information as well as the results of their history, presentation, examination, imaging technique and their final diagnosis depending on the histopathology reports. The results were analyzed finally to find the accuracy of the clinical examination, imaging technique results and cytology reports in comparison to the final results of histopathology.

Each patient visiting the breast clinic and admitted to the hospital for operation will be interviewed according to specified questionnaires, which include:-

1. History and physical examination: History includes: name, age, occupation, address … etc. Physical examination includes: Examination of both breasts and axillary. After detailed history and a thorough physical examination, the clinical impression is categorized to (benign, inconclusive, and malignant).

2. Breast imaging by ultrasound and mammography: Ultrasound; A 7.5 MHZ linear-array transducer was applied to the skin after adequate lubrication. Scan was taken both longitudinally and transversely at 2 mm intervals. Both breasts and axillae were examined and the results were interpreted by the radiologist. Digital mammography was used, all patients had medio-lateral oblique and cranio-caudal views for the diseased breast and all the results were recorded according to BIRAD sorting system.

3. FNAC done by using a disposable 10 ml or 20 ml syringe with a fine needle of 21 G, no local anesthesia was used; the contents of the syringe were then smeared on 2 slides, immediately fixed in 95% ethanol and then stained by papanicolaou stain. They were interpreted by a single cytologist and the result was reported. Some cases had the FNA under U/S guidance in the breast clinic.

All patients are admitted to the hospital and have either excisional biopsy to confirm the diagnosis or the recommended surgical treatment. The histopathology was taken as the definite conclusive diagnosis in our analysis.

Results

One hundred and fifty six patients were included in this study; there were 117 (75%) benign lesions and 39 (25%) malignant lesions, (Figure 1).

Associated findings in history show that; pain was present in 69/156 (44.2%) of patients; of which, 65/117 (47.9%) were benign breast lesions and 4/39 (10.3%) were malignant breast lesions. Nipple retraction and history of smoking were only found in malignant breast lesions 6/39,

2/39 (15.4% and 3.3%) respectively. Nipple discharge was found in 12/156 cases (7.7%), 10 were benign representing 8.5% of benign cases. Contraceptive pills intake was more in malignant breast lesions (61.5%), while lactation with lower percentage of malignancy 12 (30.7%) compared to those who have benign breast lumps (32.4%), (Table 1).

Most of lesions have well circumscribed contour (72.4%); all malignant lesions have Ill-defined contour (100%) and (3.4%) were seen in benign lesions, all malignant masses have speculated margin while (98.3%) of benign masses have smooth margins, hypoecogenicity was main feature of malignant masses (94.9%), while benign features have mainly hyperecogenicity (73.5%). Malignant masses have mainly taller than broader in diameters (94.9%), (Table 2).

All of the malignant masses were irregular in outline and ill-defined in contour while (86.3%) of benign masses were regular and (95.7%) were well defined. About (92.3%) of malignant masses were heterogeneous and (84.6%) of them dense radiographically, most of the malignant masses were amorphous (92.3%), (Table 2).

Micro-calcifications were very evident radiologic signs in malignant diagnosis (82.1%) in comparison to absence in benign masses, as the majority shown no calcification (88.9%). Both malignant and benign masses were not associated with thickening of overlying skin in the vast majority of them. The effect of breast masses on nipple most was of little magnitude especially for benign masses (1.7%) but more marked for malignant masses (10.3%), (Table 3).

The histopathological diagnosis was available in all 156 patients. There were 39/156 (25%) malignant cases 34/39 (87.1%) proved to be invasive ductal carcinoma, and 5/39 cases (12.8%) were invasive lobular carcinoma. Of the benign breast lesions, the most common lesion was Aberration of normal development and involution (ANDI), which includes 33/117 (28.2%) cases followed by; fibroadenoma 30/117 (25.6%), acute mastitis 20/117 (17.1%), chronic mastitis 14/117 (12%), benign breast cyst 6/117(5.1%), duct ectasia 6/117(5.1%), benign ductal papillomatosis 4 cases (3.4%), 3 cases for Lipoma (2.6%) and one case for phylloides tumor (0.9%), (Table 4) .

Clinical examination (C/E), ultrasonography (U/S) and mammography and fine needle aspiration cytology (FNAC) were done in all patients, and the results were categorized into two groups: benign and malignant, (Figure 2).

For the 39 cases proven to be malignant by histopathological examination, the results of 8 false negative was for C/E, 4 false negative for U/S, 5 false negative for mammography, 3 for FNAC, and 2 false negative for triple assessment. The sensitivity figure which is based only on the true malignant describes the ability to make a true positive diagnosis. The study shows that U/S has a higher sensitivity (89.7%) for cancer than mammography (87.2%) than clinical examination (79.5%) and slightly lower than FNAC (92.3%). For the 117 breast mass to be proven benign lesions on histopathology, the results of false positive results were 12 for C/E, 4 false positive for U/S and 5 false positive for mammography and two for FNAC. The specificity for the C/E was (89.7%), for the U/S (96.6%), for mammography (95.7%), for the FNAC (98.3%) and the triple assessment was (100%), (Table 5).

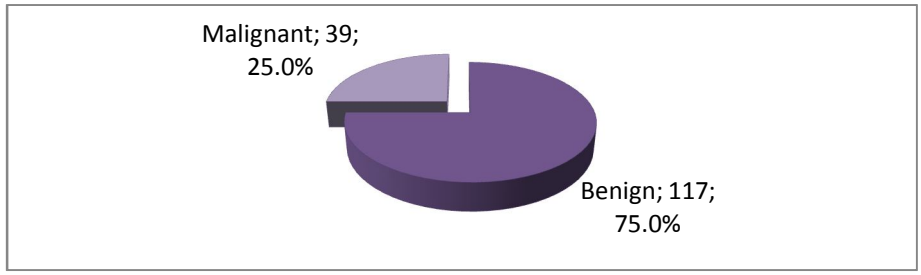

Figure 1: The type of breast lesions in the study sample proved by histopathology.

Table 1: Findings of breast lumps at presentation.

Associated findings	Benign		Malignant		Total		P value
	No.	%	No.	%	No.	%	
Pain	65	47.9	4	10.3	69	44.2	0.0001*
Nipple retraction	-	-	6	15.4	6	3.8	-
Nipple discharge	10	8.5	2	3.3	12	7.7	0.488
Skin changes	19	16.2	5	5.1	24	15.4	0.608
Trauma	2	1.7	-	-	2	1.3	-
Family history	18	15.4	6	15.4	24	15.4	0.999
Contraceptive pills use	12	10.3	24	61.5	36	23.1	0.0001*
Lactation	38	32.4	12	30.7	50	32.1	0.843
Smoking	-	-	2	3.3	2	1.3	-

*Significant using Pearson Chi-square test at 0.05 level of significance.

Table 2: The differences in mass characteristics between benign and malignant diagnosis on breast ultrasonography.

Character	Benign (n=117)		Malignant (n=39)		Total (n=156)	
	No.	%	No.	%	No.	%
Mass contour						
Well circumscribed	113	96.6	-	-	113	72.4
Ill-defined	4	3.4	39	100	43	27.6
P value			-			
Echogenicity						
Hypoechoic	4	3.4	37	94.9	41	26.3
Isoechoic	27	23.1	2	5.1	29	18.6
Hyperechoic	86	73.5	-		86	55.1
P value			0.0001*			
Margins						
Smooth	115	98.3	-	-- -	115	73.7
Speculated	2	1.7	39	100	41	26.3
P value			-			
Form of mass						
Nodular	11	9.4	35	89.7	44	28.2
Elliptical	77	65.8	3	7.7	80	51.3
Amorphous	29	24.8	1	2.6	30	19.2
P value			0.0001*			
Maximum diameter of mass						
Taller than Broader	2	1.7	37	94.9	39	25
Broader than Taller	115	98.3	2	5.1	117	75
P value			0.0001*			
Axillary lymph nodes involvement	-	-	17	48.6	17	10.9

*Significant using Pearson Chi-square test at 0.05 level of significance.

Table 3: The differences in other breast findings between benign and malignant diagnosis on breast mammography.

Character	Benign (n=117)		Malignant (n=39)		Total (n=156)	
	No.	%	No.	%	No.	%
Calcification						
Absent	104	88.9	5	12.8	109	69.9
Macro	13	11.1	2	5.1	15	9.6
Micro	-	-	32	82.1	32	20.5
P value			0.0001*			
Thickening of skin						
Negative	99	84.6	34	87.2	133	85.3
Positive	18	15.4	5	12.8	23	14.7
P value			0.696			
Nipple Retraction						
Negative	115	98.3	35	89.7	150	96.1
Positive	2	1.7	4	10.3	6	3.9
P value			0.016*			

*Significant using Pearson Chi-square test at 0.05 level of significance.

Table 4: Distribution of breast lesions according to the result of their histopathology.

Type of breast lesions		No.	%Total	%Subgroup
Malignant	Invasive ductal carcinoma	**34**	21.8	87.1
	Invasive lobular carcinoma	**5**	3.2	12.8
Benign	ANDI (fibroadenosis, fibrocystic, cyclical nodularity)	**33**	21.2	28.2
	Fibroadenoma	**30**	19.2	25.6
	Acute mastitis	**20**	12.8	17.1
	Chronic mastitis	**14**	9	12
	Duct ectsia	**6**	3.8	5.1
	Benign breast cyst	**6**	3.8	5.1
	Benign ductal papillomatosis	**4**	2.6	3.4
	Lipoma	**3**	1.9	2.6
	Phyllodes tumour	**1**	0.6	0.9

* ANDI (Abbreviation of normal development and involution)

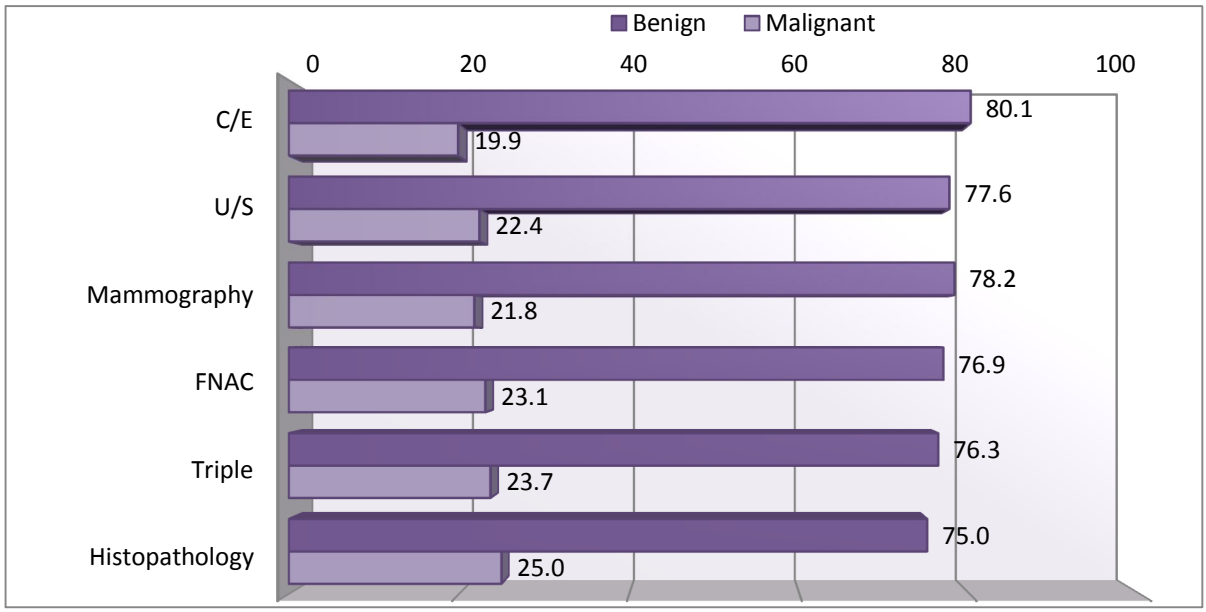

Figure 2: The results of triple assessment in percentage.

Table 5: Distribution of results of the total 156 patients with proven histopathology and the resulted sensitivity and specificity.

Results		Histopathological diagnosis				P value	Kappa test
		Benign		Malignant			
		No.	%Specificity	No.	%Sensitivity		
C/E	**Benign**	105	89.7	8		0.0001*	0.669
	Malignant	12		31	79.5		
U/S	**Benign**	113	96.6	4		0.0001*	0.863
	Malignant	4		35	89.7		
Mammo	**Benign**	112	95.7	5		0.0001*	0.829
	Malignant	5		34	87.2		
FNAC	**Benign**	115	98.3	3		0.0001*	0.914
	Malignant	2		36	92.3		
Triple	**Benign**	117	100	2		0.0001*	0.965
	Malignant	-		37	94.9		

*Significant using Pearson Chi-square test at 0.05 level of significance.

Discussion

In the current study, we verify the results of all component of the triple test according to histopathological examination of tissue specimens obtained via appropriate surgical procedure. Each element is scored prospectively in the same fashion as either benign or malignant and statistically finds the parameters of sensitivity and specificity.

The first part of triple test is the physical examination. This was done in all patients who presented with breast mass. In our study, in comparing with their histopathological reports, the sensitivity was (79.5%) and the specificity was (89.7%). These results are close to a study in King Fahad Hospital (Al-Mulhim AS reported (82.6%) sensitivity, (97.3%) specificity[9], and also to Mulago Hospital, Kampala, Uganda. The sensitivity and specificity of clinical examination were 89.3% and 88.2%, respectively[10].

In the present study, the U/S sensitivity and specificity were (89.7%) and (96.6%) and mammography (87.2%) and (95.7%) respectively were close to a study by J A

Smallwood et el[11] and Robert L Egan[12], respectively.

In a study by Baker LH, showed that the usage of U/S has false-negative results in 5% to 15% of patients with palpable breast cancers, especially in younger patients with mammographically dense breast tissue and in the lobular cancers that are not normally associated with microcalcification[13].

Ultrasound and digital mammography were done in all our patients unlike the conventional, the digital mammography has screen-field imaging with better image quality and fewer artifacts, and requires fewer patient recalls[14].

In a study by Houssami, he examined the influence of knowledge of mammographic findings on the accuracy of ultrasound in women with breast symptoms. For one reader, sensitivity increased from 77.5% to 86.7% (p = 0.0002) and specificity decreased from 89.7% to 85.4% (p = 0.04). His study indicates that knowledge of the findings of mammography improves the interpretation of breast ultrasound in symptomatic women[15].

Screening mammography is used to detect unexpected breast cancer in asymptomatic women. An experienced radiologist can detect breast cancer with a false-positive rate of 10% and a false-negative rate of 7%[16].

J A Smallwood et al found the use of ultrasound in comparing to mammography to be both more sensitive (93%:82%) and specific (95%:89%). In this study, the greater accuracy of ultrasound was attributed to its ability to diagnose lesions hidden in X-ray dense breasts and where mammography had revealed featureless asymmetrical densities of uncertain nature. In these instances ultrasound may have a significant role to play as an adjunct to mammography in the preoperative assessment of breast lesions[11].

The FNAC has been proposed as reliable, cost saving, painless, repeatable and quick initial procedure for preoperative diagnosis of palpable breast lesions and as an alternative to open biopsies[17].

In this study, there were three false negative and two false positive in FNAC results, the sensitivity and specificity were (92.3%) and (98.3%), respectively. In Shifa International Hospital, Islamabad, FNAC results included two false negative and 0 false positive[18], while in other study by Troxel DB, the sensitivity and specificity were (95%) and (96%) respectively[19].

The false negative rate, a limitation of FNA cytology, has become the center of focus in litigation cases, accounting for 10% of all pathology-related malpractice which was concluded by Troxel DB et al[19].

Major factors contributing to a false negative cytological diagnosis include inadequate cellularity that may be due to misdirected sampling, a misinterpretation of cells aspirators insufficient needle maneuvers, needle withdrawal under negative pressure, lack of forcible specimen ejection on to the slide and less than optimal fixation methods[19].

We have used the triple test in the management of these 156 patients and in all patients we depended on the results of this triple test assessment, all patients had the correct diagnosis with the correct management except two patient in whom the triple test showed a benign result and the definitive management changed to a modified radical mastectomy when the result of excisional biopsy revealed invasive lobular carcinoma and other Invasive ductal carcinoma.

In many studies, Katherine T Morris et al[20], Al-Mulhim AS et al[9], Ahmed I et al[18], the triple test was 100% accurate in the diagnosis of palpable breast lesions with sensitivity (100%) and specificity (100%) when all three elements were concordant. These results are not far from our study. The sensitivity was (94.9%) and the specificity (100%). Therefore we can regard the triple assessment as a powerful clinical tool that permits rapid, minimally invasive, and accurate diagnosis of palpable breast masses. We could recommend elimination of the confirmatory open biopsy, which will result in reduced expenses and morbidity compared with open biopsy.

Triple diagnosis refers to the concurrent use of physical examination, mammography and U/S and skilled FNAC for diagnosing

palpable breast lumps, especially solid lumps. Very few breast cancers are missed using triple assessment. In a study by Layfield, only 0.7% of women had breast cancer when all three tests suggested benign lesions, while the rests of women in whom all three tests were positive had breast cancer. In a second report for the same study, triple diagnosis was more cost-effective than subjecting all women with a palpable breast lump to open biopsy[21].

Accurate diagnosis without resorting to pre-operative biopsy enables the patient to have appropriate counseling before definitive surgery. Furthermore, valuable operating time is not wasted and the waiting list is arranged so that the more serious patients have their operations first. Even a solid diagnosis with a short time can be achieved with a simple, easy, fast, minimally invasive, Low-cost assessment system. This will decrease the patient's anxiety. Nevertheless, the emphasis must be on the avoidance of unnecessary ablative surgery. Hence, in this study, the accuracy of triple test in improving reliable pre-operative diagnosis was investigated.

According to the results of this study, we think the following protocol can be used with the triple diagnosis approach; Women in whom all three tests suggest benign disease must be followed up until we make sure the mass is stable or regressed. Women in whom all three tests suggest malignancy must be referred for definitive therapy. Women with any one of the tests suggesting malignancy should undergo excisional biopsy.

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