

Evaluation of Triple Assessment Modalities in the Management of Palpable Breast Lumps

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ABSTRACT:

BACKGROUND:

Breast masses are common clinical presentation in breast clinics, their managements require an efficient and accurate evaluation, using the least invasive, most accurate methods that cause minimal patients discomfort and limit any unnecessary procedure.

OBJECTIVE:

This study is designed to evaluate the diagnostic accuracy of triple assessment (a combination of clinical examination, imaging studies and tissue sampling) in the preoperative assessment and optimal management of palpable breast masses.

PATIENTS AND METHODS:

This clinical prospective study which was conducted in mosul breast center, department of surgery, al-jamhoory teaching hospital, mosul medical city, from november 2007 to november 2008 included 60 female patients with palpable breast masses, their age ranging between (20-76) years, were assessed prospectively using triple assessment modalities and the results of each modality were classified as benign, suspicious or malignant and compared with the confirmatory histopathological examination of the tissue specimens obtained from all patients under study via an appropriate surgical procedure. the data was collected, classified and analyzed.

RESULTS:

The results triple test (TT) was concordant (elements had either all benign or all malignant) in 31 cases (52%) with diagnostic accuracy reaching (100%). Again the TT achieved (100%) diagnostic accuracy when all elements were either malignant or suspicious which appeared in 12 of 29 nonconcordant cases (20% of all cases). FNAC was the most reliable element of TT in cases where the elements of TT weren't concordant (NPV 94.5%, sensitivity 92% and accuracy 96.7%).

CONCLUSION:

The TT has proved to be accurate, reliable diagnostic approach for evaluation of breast masses, achieved (100%) accuracy rate when all elements were concordant or when all elements were either suspicious or malignant, with the end result was neither missed cancer nor false positive malignant diagnosis, as the error or limitation of one modality was compensated by the other elements.

Any positive result of fnac should be taken seriously with negative results not exclude malignancy while the negative or positive results of imaging studies and examination not necessarily reflect the actual pathology should be supported by tissue diagnosis.

Patients in whom the TT elements were all benign can be safely observed, while patients in whom all the elements were malignant or suspicious, the diagnosis was certain enough to proceed with definite treatment without delay.

KEYWORDS: breast masses, fnac, mammogram, ultrasound, triple test.

INTRODUCTION:

Breast masses are common clinical presentation in breast clinics, have variety of etiologies, benign or malignant, their management and prognosis depend on early diagnosis and prompt treatment⁽¹⁾. The

diagnostic approach of palpable breast lumps should involve the use of rapid, inexpensive, most accurate and least invasive methods to evaluate and distinguish between benign and malignant lumps in out patient clinics, such methods would benefit both patients and surgeons by

- Promoting proper preoperative diagnosis and management.
- Further limits unnecessary testing and procedures^(2,3,4).

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Evaluation of Breast Masses

The general approach to evaluation of breast masses or other symptoms suspicious of carcinomas has become formalized as triple assessment, involving a combination of Clinical assessment (history and examination), Imaging studies (usually ultrasound and or mammography) and Tissue sampling taken for either (cytological or histological) analysis^(3,4).

The aim of evaluation is to avoid missing malignant lesions, provides reassurance in benign conditions and determines what treatment if any, is indicated.

PATIENTS AND METHODS:

The study sample consisted of (60) female patients, their age ranging between (20 – 76) years with mean age of (43) years, most of the patients were referred from the specialized breast center (sbcc) in the out patient department of al-Jamhoory teaching hospital, during the period from november/ 2007 – november / 2008.

The criterion for patients eligibility was the presence of clinically palpable localizing lesion differing from the surrounded breast tissue, each patient was assessed prospectively by physical examination (PE), mammography (MG) and/ or ultrasound (US) and FNAC (triple assessment modalities), The results of each modality were reported independently of one another and assigned as either malignant, Benign or suspicious and compared with the conclusive diagnosis (standard criterion) which was the histopathological results of tissue specimens obtained from open biopsy, lumpectomy or mastectomy of the breast mass under study.

Exclusions included patients who didn't have a combination of physical examination, Imaging study or FNAC or for whom the results of all three elements of triple test weren't clearly recorded and also patients in whom no definable mass could be detected both on clinical examination and imaging evaluation.

Clinically the term malignant mass was applied to a breast lump with obvious malignant signs as hard, Non tender, Lump, Fixed to chest wall or

surrounding tissues with peau d'orange, Skin tethering, Axillary or supraclavicular lymph nodes enlargement and nipple retraction, The clinically suspicious masses were regarded as a malignant masses and both underwent TNM clinical staging system classification.

Mammographic examination was done for all patients aged 30 years and more with two standard views craniocaudal and mediolateral oblique for the affected breasts and craniocaudal views for the opposite breasts.

All the patients with breast masses underwent ultrasonographic assessment using a hand held 7.5MHZ linear-array probe and the findings classified breast masses into malignant, benign or suspicious.

FNAC was done by expert pathologists for all sample, after the imaging evaluation to avoid confusing with small haematoma that may result from FNAC, using 10ml disposable syringes with 21–23 gauge needles and no local anesthesia, The results of the triple tests were classified and statistically analyzed using the following measures, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Accuracy, The student t-test to assess difference between two means was used for continuous data (age, duration,...) and the Chi-square (χ^2) test for contingency tables. During statistical analysis P-value >0.05 was considered non significant, P-value ≤ 0.05 was considered significant and P-value < 0.001 the result was highly significant.

RESULTS:

A total of sixty females with palpable breast lesions that fulfilled the study criteria underwent diagnostic evaluation using triple assessment modalities. All the lumps were subsequently subjected to surgery, of which 35 out 60 (58.4%) were proved to be benign and the remaining 25 (41.6%) were proved to be malignant on the histopathological examination as shown in table (1).

Table 1: Distribution of patients in relation to the histopathology of breast masses

Patient No.	Histopathology	% of total sample
25	Malignant	41.6
35	Benign	58.4
60	Total	100

The mean age of patients was (42.6) years with age ranged from (20-76) years as shown in table(2).

Table 2: Distribution of all patients according to the age groups.

Age group (years)	No. of patients	% of total sample
15 – 25	9	15
26 – 35	10	16.6
36 – 45	21	35
46 – 55	11	18.3
56 – 65	5	8.3
66 – 75	3	5
76 – 85	1	1.6
Total	60	100

The age range for patients with malignant breast masses was (25-76) years with mean age of (50.5) years and SD $\pm$ (10.09) years with age ranged from (20-64) years, Student t-test =4.945 with P-value < 0.001 for age difference as shown in table(3).
for patients with benign lesions was (36)

Table 3: Distribution of patients with malignant and benign breast masses according to the age.

Age group (years)	Malignant masses			Benign masses		
	No. of patients	%	% of total sample	No. of patients	%	% of total sample
15 – 25	1	4	1.6	8	22.8	13.3
26 – 35	2	8	3.33	8	22.8	13.3
36 – 45	6	24	10	15	42.8	25
46 – 55	8	32	13.3	3	8.5	5
56 – 65	4	16	6.6	1	2.8	1.6
66 – 75	3	12	5	/	/	/
76 – 85	1	4	1.6	/	/	/
Total	25	100	41.6	35	100	58.4

Student t-test =4.945 , P-Value < 0.001

About (65%) of all cases of breast cancer has occurred in women over the age of 45 years, While most of patients with benign breast masses (about 43%) belong to the (36-45) age group.

Tables (4), (5), (6) and (7) respectively showed the relation between the results of CBE(clinical breast examination), MG, US and FNAC and the histopathological confirmation

Table 4: Physical Examination versus histopathology results.

Histopathology	Physical Examination			
	Malignant	Benign	Suspicious	Total
Malignant	5	3	17	25
Benign	3	28	4	35
Total	8	31	21	60

$\chi^2=27.815$, P-Value < 0.001

Table 5: Mammogram versus histopathology results.

Histopathology	Mammogram			
	Malignant	Benign	Suspicious	Total
Malignant	16	3	6	25
Benign	2	23	2	27
Total	18	26	8	52

$\chi^2=28.238$, P-Value < 0.001

Table 6: Ultrasound versus histopathology results.

Histopathology	Ultrasound			
	Malignant	Benign	Suspicious	Total
Malignant	14	2	9	25
Benign	1	33	1	35
Total	15	35	10	60

$\chi^2=44.699$, P-Value < 0.001

Table 7: FNAC versus histopathology results.

Histopathology	FNAC			
	Malignant	Benign	Suspicious	Total
Malignant	19	2	4	25
Benign	0	35	0	35
Total	19	37	4	60

$\chi^2=52.216$, P-Value < 0.001

The sensitivity, specificity, PPV, NPV and accuracy of PE, MG, US, FNAC and the TT as whole have been calculated considering suspicious cases as malignant as shown in table (8).

Table 8: Analyses of triple test (TT) and it's components for (60) cases of palpable breast masses.

Measure	PE	MG	U/S	FNAC	TT	PE+MG	PE+FNAC	PE+US
Sensitivity	88 %	88%	92%	92%	100%	96.1%	96%	100%
Specificity	80%	85.1%	94.2%	100%	71.4%	74.3%	80%	77%
PPV	75.8%	84.6%	92%	100%	77.4%	72.7%	77.4%	76%
NPV	90.3%	88.4%	94%	94.5%	100%	96.3%	96.6%	100%
Accuracy	83.3%	86.5%	93.3%	96.7%	83.3%	83.3%	86.7%	86.7%

The TT was scored as concordant (in agreement), If the elements had either all malignant or all benign results.

The TT was considered non concordant, If the elements had neither all malignant nor all benign results, the results of TT compared to histopathology results are shown in table (9)

Table 9: Results of the triple tests for (60) palpable breast lesions and histopathology confirmation.

Triple test results		No. of lesions	Histopathology results		Total		χ^2	P-Value
			Benign	Malignant	No.	%		
Concordant	Benign	25	25	0	25	42	31.000	< 0.001
	Malignant	6	0	6	6	10		
Non-concordant	Suspicious	29	10	19	29	48	/	/
Total			35	25	60	100	13.137	< 0.001

As illustrated in the above table, The TT was concordant in 31cases (52%), In 25 of these lesions (42%), The results of all elements of TT were interpreted as benign and subsequently were proved to be benign pathologies histologically with NPV and Specificity scored 100%.Similarly, in 6 cases (10%) in which the results of all elements of TT were interpreted as malignant and proved to be malignant lesions on histopathological examination, the sensitivity and PPV were 100 % , TT elements were non concordant in 29 cases (48%), 19 of these cases were proved to have malignant masses and the

remaining 10 cases were proved to be benign on subsequent histopathological examination with PPV of (65.5%), Among the 17out of 29 non concordant cases, Where at least one of the elements was considered benign, FNAC was the most accurate [2 false negative(FN) and 0 false positive(FP)] results as shown in lines ^(9,12), table (10).

A more detailed listing of 29 non concordant in cases is presented in table (10), if the results of all three elements were suspicious or malignant, the test was again 100% PPV, this has occurred in 12 out of 29 non concordant cases [lines 1-5/ table(10)]

Table 10: Detailed results of (29) cases of non concordant triple tests for palpable breast lumps.

Line No.	Tests results of non concordant cases					Histopathology	
	Physical examination	Mammography	Ultrasound	FNAC	Sum	Malignant	Benign
1	S	S	S	M	3	3	0
2	S	M	S	M	4	4	0
3	S	M	M	S	2	2	0
4	M	S	M	M	2	2	0
5	S	M	M	M	1	1	0
6	S	M	B	S	1	1	0
7	S	M	B	M	1	1	0
8	B	B	S	M	1	1	0
9	B	M	M	B	1	1	0
10	S	B	S	M	1	1	0
11	B	S	M	S	1	1	0
12	S	B	M	B	1	1	0
13	S	B	B	B	4	0	4
14	M	M	M	B	1	0	1
15	B	S	B	B	2	0	2
16	B	B	S	B	1	0	1
17	M	M	B	B	1	0	1
18	M	B	B	B	1	0	1
Total					29	19	10

S: suspected malignancy; M: malignancy; B: benign

For benign masses, fibroadenomas were the predominant lesions and formed (28.5%) of benign breast masses followed by fibrocystic disease (22.8%), inflammatory conditions (abscesses, antiabioma, mastitis) (20%), ductectasia (11.4%), fibroadenosis (8.5%) and lastly duct papilloma, granulomatous mastitis and lipoma each formed (2.8%) of benign breast masses, as shown in table(11).

Table 11: Distribution of patients according to types of benign breast disease

Benign breast disease	No. of patients	% of benign masses	% of total masses
Fibroadenoma	10	28.5	16.6
Fibrocystic disease	8	22.8	13.3
Inflammatory process	7	20	11.6
Duct ectasia	4	11.4	6.6
Fibroadenosis	3	8.5	5
Duct papilloma	1	2.8	1.6
Lobular granulomatous mastitis	1	2.8	1.6
Lipoma	1	2.8	1.6
Total	35	100	58.4

From malignant breast masses, invasive ductal carcinomas (IDC) were the most common pathological diagnosis (19 out of 25 cases), Forming (76%) of malignant breast masses followed by invasive lobular carcinomas (ILC) (12%), malignant phylloid tumour (8%) and one case was a carcinoma in situ (4%), as shown in table(12).

Table 12: Distribution of patients according to the types of malignant breast disease

Malignant breast disease	No. of patients	% of malignant masses	% of total masses
Invasive ductal carcinoma	19	76	31.6
Invasive lobular carcinoma	3	12	5
Malignant phylloid tumour	2	8	3.3
Carcinoma in situ	1	4	1.6
Total	25	100	41.6

Regarding associated features, lymph nodes enlargement was the main malignancy associated findings occurred in 13 out of 25 cases (52%) of patients with malignant breast masses compared to 5 cases (14.2%) in patients with

benign breast masses, for which the pain was the most frequent associated feature occurred in 14 out of 35 (40%) cases of benign breast lesions, compared to 20% (5 of 25) of malignant masses, as shown in table (13).

Table 13: Breast masses associated features.

Associated feature	Malignant masses		Benign masses		Total masses		χ^2	P-Value
	No.	%	No.	%	No.	%		
Pain	5	20	14	40	19	31.4	2.696	< 0.101
Discharge	3	12	11	31.4	14	23.3	3.077	< 0.079
Nipple retraction	4	16	5	14.2	9	15	0.038	< 0.855
Skin tethering	12	48	4	11.4	16	26.6	9.974	< 0.002
L.N. enlargement	13	52	5	14.2	18	30	9.987	< 0.002

DISCUSSION:

Regarding the age, about (65%) of all cases of breast cancer has occurred in women over the age of 45 years, and was rare in teenagers (only one patient) and uncommon among women under the age of 30 years (3 patients only), So it's typically a disease of older age groups, The age range for patients with malignant breast masses was between (25-76) years with mean age of breast cancer in this study was 50.5 years compared to 36 years for patients with benign lesions, The age difference is statically significant ($p < 0.001$).

These findings was documented by bailey and love's⁽⁵⁾, browse's⁽⁶⁾ and cuschieri⁽⁷⁾, Al-Alwan⁽⁸⁾, bilal⁽⁹⁾, and al-chetachi⁽¹⁰⁾.

For malignant breast masses, IDC (invasive ductal carcinoma) in this study was the most common malignant pathology and constituted (76%) of all malignant masses followed by ILC which formed (12%). For benign masses, the fibroadenoma was the predominant lesion, formed (28%) of all benign masses followed by fibrocystic disease (22.8%). These finding were also reported by bilal⁽⁹⁾, schwartz's⁽¹¹⁾, Al-Alwan⁽⁸⁾

In this prospective study, analysis of the results obtained showed that, when the TT was concordant (in agreement) as seen in 52% (31 patients) or when all the three elements of the TT were either suspicious or malignant which was appeared in (20%) of cases (non concordant), the diagnostic accuracy predicted by the TT reached (100%) which was found in 31 concordant cases and 12 of non

concordant cases (total 43 of 60 cases) (72% of the all sample). The (100%) diagnostic accuracy achieved when all three elements of TT were concordant has also been reported in other studies conducted by Vetto et al⁽¹²⁾, Grobler et al⁽¹³⁾ and Al-Alwan⁽⁸⁾. When the elements of TT were non-concordant, the overall diagnostic accuracy of TT achieved in this study was (65.5%) which was more or less similar to the accuracy rates reported in studies conducted by Vetto et al⁽¹²⁾, grobler et al⁽¹³⁾ and Al-Alwan⁽⁸⁾ that reported diagnostic accuracy of (64%, 75% and 57%) respectively when the TT was non-concordant.

In this research, FNAC proved to be the most accurate element of the TT with 2 FN results and no FP results in 17 out of 29 of non-concordant cases, Where at least one of the elements was considered benign. The 2FN results one proved to be mucoid carcinoma (a variety of ductal carcinoma) and other was lobular carcinoma on subsequent histological examination. The FN diagnosis of invasive lobular carcinoma can be explained to be due to sampling problem as the ILC are composed of separated, usually small uniform cells compared to invasive ductal carcinoma result in paucicellular smear with a poor yield of cells on FNAC^(14,15). The FN diagnosis of mucoid tumor was attributed to interpretation errors, as mucoid cancer is one of a well differentiated carcinomas and FN may occur because individual cells sometime lack the obvious malignant changes⁽¹⁶⁾.

Ultrasound was the next most accurate test in this study after FNAC, had 2FN, Proved on subsequent histopathological confirmation to be DCIS and IDC respectively and 2FP (lines14,16)which were proved to be fibroadenosis and antibioma respectively on histological examination, these contributed to the facts that US is an operator dependent and there is a significant overlap in the appearance of benign and malignant palpable solid breast masses as a round well circumscribed carcinoma with homogenous tissue texture can look identical to a benign breast lesion, and benign lesions can have the classic malignant appearance of an irregular shaped structure with an inhomogeneous or absent echotexture with posterior shadowing^(5,17,18). Similar conclusions has been reported by Rosner et al⁽¹⁹⁾ and Van Dam et al⁽¹⁸⁾. Mammography was the next accurate imaging modality in this research with 4FP and 3FN results, table (10), the 4FP results appeared on MG were proved subsequently to be 2 cases of fibrocystic disease, 1 case ductectasia and 1 case granulomatous mastitis on the histopathological examination, with 3 FN results that were proved subsequently on histological examination to be 1 case IDC, 1 case ILC and 1 case malignant phylloid tumour. Again this was connected to the overlapping features of benign and a circumscribed well defined malignant breast lesion and to the fact that dense breast tissue has been mentioned as an important obstacle in the mammographic diagnosis and a source of number of FN diagnosis^(20,17) These findings have been supported by similar results reported in other studies conducted by Kopan⁽¹⁷⁾, Kreuzer et al⁽²¹⁾, van Dam et al⁽¹⁸⁾ and Al-Chetachi⁽¹⁰⁾.

In the present study, the physical examination had the lowest accuracy rate among all other elements of TT (83.3%) with 3FN (lines 8,9,11) and 7FP (lines13,14,17,18) results, This reflected the overestimation of malignancy by this modality as it's obviously that all breast lesions under study were palpable and that diagnostic criteria were deliberately chosen at a low threshold, resulting in a high FP rate and clinical assessment of breast masses, in particularly of a deep seated and/or minor one evidently involves greater uncertainty than imaging and histological examination, resulting in poor discrimination to the nature of the detected mass. Lymph nodes enlargement was the main malignant masses concurrent findings, Found in 13 cases (52%) of the patients with malignant masses compared to (14.3%) of patients with benign masses, The more frequently LNs involvement in

relation to malignant breast lesions due to mainly secondary deposits and partly to reactive hyperplasia, these findings also consistent with the findings of studies conducted by Hassan⁽²²⁾ and Bilal⁽⁹⁾. Other clinical features including pain, discharge, nipple retraction, skin tethering....etc, are neither specific nor determinant to the types of breast lesions as indicated by p-value and should be assessed as a part of the TT.

In this research, for suspicious masses in which the results of all elements of Triple Test were malignant or suspicious, the results of all histopathological examination of the tissue specimens taken from these breast masses (via excisional biopsies or true cut biopsies) were malignant with positive predictive value(100%), this was seen in 12 patients form (20%) of all sample and (41%) of nonconcordant cases, while for suspicious masses in which the results of elements of Triple Test involved a combination of (benign plus malignant or suspicious results) were seen in 17 patients [(59%) of nonconcordant cases] and the results of histopathological analysis showed benign results for some of these masses (10 patients) and malignant for others(7 patients).

So, in the present study, the above results signify the importance of performing open biopsies when the elements of Triple Test involved a combination of (benign plus malignant or suspicious results) to settle the diagnosis prior to any treatment, while their role in suspicious masses in which the results of the elements of Triple Test were all malignant or suspicious are confirmatory.

Concerned suspicious masses, Vetto et al⁽¹²⁾ recommended that confirmatory open biopsies can be avoided for suspicious masses (defined in his study as lesions in which the results of the elements of Triple Test were nonconcordant) when the results of FNAC and one other elements of Triple Test are malignant or suspicious as this approach resulted in no missed cancers in the above study and no false positive malignant diagnoses, these results are more or less similar to the results in the present study.

Contrary to that, Rubin et al⁽²³⁾ recommended that highly suspicious masses(defined in his study as lesions classified by two of three elements of Triple Test as malignant or suspicious) should undergo excisional biopsy prior to treatment in the case in which FNAC is either suspicious or negative and

can obviate the need for biopsy prior to treatment in the case of highly suspicious breast masses with malignant results on FNAC as the false positive results for FNAC in the above study were zero. Erhan et al⁽²⁴⁾ study recommended that FNAC should be repeated if the initial result was suspicious even if the results of Triple Test were malignant on imaging studies and physical examination and advised to perform open biopsy if the result of the second FNAC was still inconclusive and concluded that biopsy can be avoided if the results of imaging studies, physical examination and FNAC were positive for malignancy.

It is obvious that options regarding the optimal management of the suspicious breast masses are not in full agreement in various studies and the performance of any procedure or intervention prior to the definitive treatment is mainly still related to surgeon experience and satisfactions and the nature of condition of a particular patient.

In this study, the analysis of triple test and it's component shows the superior accuracy of FNAC and US in the evaluation of palpable breast masses and that a combination of (US+PE) and (PE+FNAC) constitute the optimal preoperative tests combination. with the end result of this study is no missed cancer and no false positive malignant diagnosis on using the triple assessment modalities for the diagnostic evaluation of the breast masses, as the error or limitation of one modality is compensated by the other elements.

CONCLUSION:

The triple test (PE, imaging study and FNA) appears to be the most effective, non-invasive diagnostic combination, achieving (100%) diagnostic accuracy when all the elements of the test are concordant (in agreement) or when all the elements of the test are either suspicious or malignant, it is recommended that patients in whom the triple test elements were all benign, can be safely observed, obviating the need for an open biopsy and patients with suspicious masses in whom all the elements of TT were only malignant or suspicious, the diagnosis is certain enough to proceed with definite treatment without delay.

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