Original Research Article

New Indian Journal of Surgery
Volume 9 Number 4, July - August 2018
DOI: https://dx.doi.org/10.21088/nijs.0976.4747.9418.19

Triple Test Approach for Diagnosis of Palpable Breast Lesions

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How to cite this article:

Gautam N. Gole & Sheetal G. Gole. Triple Test Approach for Diagnosis of Palpable Breast Lesions. New Indian J Surg. 2018;9(4):498-02.

Abstract

Introduction: Management of breast diseases is a multidisciplinary endeavor dependent on skill and expertise of an array of clinical specialists. Study evaluates efficacy of the individual components of triple test in diagnosis of palpable breast lesions. *Materials and Methods:* Present study was a hospital based prospective study done over a period of 2 years and included 100 female patients with palpable breast lesions in a tertiary care hospital at Telangana. Detailed clinical history and physical examination was done, followed by mammography, fine needle aspiration cytology. The histopathological report was considered the reference standard. *Results:* Triple test is the combination of clinical examination, mammography and fine needle aspiration cytology. If all the 3 tests were benign then triple test was concluded as benign, and if all 3 tests were malignant then it was concluded as malignant. Triple test revealed 97.29% sensitivity and 98.41% specificity, with 1 false positive and false negative each. Triple test was scored as concordant if all the 3 tests, had either all malignant or all benign results. Triple test was scored as non-concordant if all the 3 tests had neither all malignant nor all benign results. Triple test was concordant in 82 (82%) cases. *Conclusion:* Triple Test is a powerful clinical tool that is, easy to perform, minimally invasive, and provides rapid, cost-effective, reliable, and accurate diagnosis of breast malignancies. Triple Test Score is safe and efficacious for establishing diagnosis and managing the ever-increasing number of patients presenting with breast masses.

Keywords: Clinical Breast Examination; Mammography; Fine Needle Aspiration Cytology; Triple Test; Triple Test Score.

Introduction

The commonest clinical presentation in majority of breast pathology is a lump. A breast lump may be either benign or malignant. A definite diagnosis of breast lump is of utmost importance for the surgeon to decide on the final course of treatment. It alleviates the patient from unnecessary physical, emotional, and psychological trauma if there is a definite preoperative diagnosis of benign lesion. The nature of breast lump cannot be diagnosed accurately only on clinical examination. The accuracy of diagnosis of breast cancer on physical examination is only 70% even in the most experienced hands [1].

To come to a definite diagnosis, clinical judgement needs to be supported by specialized tests. Currently two techniques are available that have excellent patient tolerability. These tests are mammography and fine needle aspiration cytology (FNAC).

Hence, management of breast diseases is a multidisciplinary endeavor dependent on skill and expertise of an array of clinical specialists: surgeons, radiologists, and pathologists.At the outset and often at later critical points, an accurate histopathological diagnosis is the crucial element for determining the course of treatment and for estimating prognosis. The present study evaluates efficacy of individual parameters of triple test: clinical breast examination (CBE), mammography, FNAC in diagnosis of palpable breast lesions.

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Received on 03.04.2018, **Accepted on** 23.04.2018

Aims & objectives

- To determine the efficacy of triple test in the form of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy in evaluation and characterization of palpable breast lump.
- To determine the efficacy of triple test score in evaluation of palpable breast lump.

Materials and Methods

Present study was a hospital based prospective study done over a period of 2 years and included 100 female patients with palpable breast lesions, who attended the outpatient department (OPD) of General Surgery in a tertiary care hospital at Telangana. A total of 148 females with breast lump were studied in Department of Surgery. But 48 patients had lost to follow-up (30 patients did not report to Surgery OPD after first consultation, and 18 patients were not willing for surgery), hence 100 patients were included in the study. Detailed clinical history and physical examination was done, followed by mammography, fine needle aspiration cytology (FNAC) and histopathological examination (HPE). Results of triple tests were correlated with histopathological examination of breast lump.

Clinical breast examination included physical examination of breast in a standard manner, with patient sitting. Breasts were inspected for asymmetry, skin retraction, ulceration or edema and then palpated. A note was made of the quadrant in which the lump was present and the measurements of the same were noted. Both the breasts were examined to rule out presence of any other lump. The area of lymphatic drainage was examined for lymphadenopathy.

Mammogram included 2 views medio-lateral oblique and standard cranio-caudal and were read by a senior radiologist in mammographic unit (Allengers Medical Systems, Digital Mammography Machine) with perpendicular compression. In our study, classifications of the American College of Radiology (ACR) for BIRADS mammographic patterns were considered as follows: Category 1, 2 as benign, category 3 as suspicious, category 4, 5 as malignant.

FNAC was performed in the Department of Pathology after mammography. Smears obtained were stained with May Grunwald Giemsa (MGG), Papanicolaou (Pap), and hematoxylin and Eosin (H & E) stains. Cytology report was given using the standard reporting categories: benign, suspicious, malignant. Incisional/excisional/lumpectomy specimens fixed in 10% neutral buffered formalin were sent for HPE. Histopathological report was considered the reference gold standard.

Statistical Analysis

All the three parameters of triple test viz.,clinical breast examination, mammography and FNAC findings were categorized as benign, suspicious and malignant and were assigned score of 1, 2, or 3 points respectively. Triple test score (TTS) is the sum of these scores. Triple test was scored as concordant if the all 3 tests (clinical breast examination, mammography, FNAC) had either all malignant or all benign results. The Triple test score has a minimum score of 3 (concordant benign) and a maximum score of 9 (concordant malignant). Triple test was non-concordant if all the 3 tests had neither all malignant nor all benign results. Triple test was scored benign or malignant depending upon the results of 2 parameters of triple test, which means it was scored benign if two parameters had benign results and vice versa.

Values of sensitivity and specificity were determined by following formula: where TP: True positive, TN: True negative, FP: False positive, FN: False negative.

Sensitivity = TP / TP + FN

Specificity = TN / TN + FP

Positive Predictive Value (PPV) = TP / TP + FP

Negative Predictive Value (NPV) = TN / TN + FN

Accuracy = (TP + TN) / (TP + FP + TN + FN)

Error = (FP + FN) / (FP + FN + TP + TN)

Kappa = (% of observed - % expected) / (100 - % expected). Kappa statistic was calculated for individual methods and their combination. A value above 0.75 suggested excellent agreement with histology, 0.40 to 0.75 was intermediate to good agreement and below 0.40 suggested poor agreement. The data was analyzed using SPSS (Statistical Package for Social Sciences) 20.0 software package.

Results

The present study evaluates the efficacy of triple test in management of palpable breast lump. All the patients attending the Surgery OPD with complaint of palpable breast lump underwent clinical breast examination, mammography, FNAC, followed by histopathological examination in the form of biopsy.

On clinical breast examination,35 malignant lumps were diagnosed correctly, and 6 benign lumps as malignant (suspicious). The sensitivity and specificity of CBE were 94.59% and 90.47% respectively.

On mammography, 36 malignant lumps were diagnosed correctly, and 4 benign lumps were misdiagnosed as malignant (suspicious). The sensitivity and specificity of mammography were 97.29% and 93.65% respectively.

Fine needle aspiration cytology, diagnosed 36 malignant lumps. False positive cases were 3 and 1

case were diagnosed false negative. The sensitivity and specificityof FNAC were 97.29% and 95.23% respectively.

Triple test is the combination of CBE, mammography and FNAC. If all the parameters are benign then triple test was considered to be benign, and if all the parameters were malignant then it was considered to be malignant. Also, triple test was scored benign or malignant depending upon the results of the two parameters of triple test, which means it was scored benign if two parameters gave benign results and vice versa. Triple test revealed 97.29% sensitivity and 98.41 % specificity with 1 false positive and false negative case each (Table 1).

All the excised masses were subjected to histopathological examination. Fibroadenoma was the most common benign lesion (60.31%) followed by fibroadenosis (26.98%). Ductal carcinoma was the most common histopathological malignant lesion observed.

Triple test was scored as concordant if the tests (CBE, mammography, FNAC) had either all malignant or all benign results. Triple test was scored non-concordant if the tests had neither all malignant nor all benign results.Triple test was concordant in 82 (82%) cases. No discrepancy was noted with the final histopathology report. All 51 benign cases detected by the triple test were benign on HPE (100% specificity and negative predictive value), and all 31 malignant lesions detected by Triple test revealed concordance with HPE (100% sensitivity and positive predictive value). (Table 1 & 2)

Triple test was non-concordant in 18 cases (18%). Amongst these, 6 cases were malignant and 12 were benign. In 3 cases, the components of triple test were either suspicious or malignant, and these were diagnosed malignant on HPE, revealing 100% positive predictive value (Table 3).

Amongst the 15 cases, where at least one of the 3 components of triple test were benign, FNAC was most accurate (1 false negative and 3 false positive). On FNAC 1 case diagnosed as benign was diagnosed as malignant on HPE, hence false negative. Three cases diagnosed as suspicious were benign on HPE, hence false positive. Mammography revealed 1 false negative and 4 false positive cases. Clinical breast examination was least accurate with 2 false negative and 6 false positive. It is of note that in one case, where FNAC gave false negative result, the other two parameters were malignant. (Table 3)

Table 1: Statistical analysis of the parameters of triple test

Diagnosis	Clinical breast examination	Mammography	Fine needle aspiration cytology	Triple test	Triple test score
True positive	35	36	36	36	31
False positive	06	04	03	01	00
True negative	57	59	60	62	51
False negative	02	01	01	01	00
Sensitivity	94.59%	97.29%	97.29%	97.29%	100%
Specificity	90.47%	93.65%	95.23%	98.41%	100%
PPV	85.36%	90.00%	92.30%	97.29%	100%
NPV	96.61%	98.33%	98.36%	98.41%	100%
ACCURACY	92%	95%	96%	98%	100%
ERROR	8%	5%	4%	2%	0%
KAPPA	0.832	0.894	0.915	0.957	1

Table 2: Number of cases concordant with histopathological examination

Clinical breast examination	Mammography	Fine needle aspiration cytology	Histopathological examination	Number of cases (%)
Benign	Benign	Benign	Benign	51 (51)
Malignant	Malignant	Malignant	Malignant	31 (31)

Table 3: Number of cases nonconcordant with histopathological examination

Clinical breast examination	Mammography	Fine needle aspiration cytology	Histopathological examination	Number of cases
Suspicious	Benign	Benign	Benign	5
Benign	Suspicious	Benign	Benign	4
Suspicious	Benign	Suspicious	Benign	1
Benign	Benign	Suspicious	Benign	2
Benign	Benign	Malignant	Malignant	1
Malignant	Malignant	Suspicious	Malignant	3
Malignant	Malignant	Benign	Malignant	1
Benign	Suspicious	Malignant	Malignant	1

Each parameter was assigned score of 1, 2, or 3 points for benign, suspicious or malignant findings respectively. There were 62 cases with score of 3 (n=51) or 4 (n=11) which on HPE were confirmed to be benign. There were 36 cases with score of 6 or more which on HPE were confirmed to be malignant. Two cases were having score of 5, out of which 1 was confirmed benign and 1 as malignant on HPE. Thus, when the TTS was less than or equal to 4, it had a specificity of 100%, and when the TTS was greater than or equal to 6, it had a sensitivity of 100% (Table 4). FNAC was most accurate (1 FN and 3 FP); followed by mammography (1 FN and 4 FP) and CBE examination being least accurate with 2 FN and 6 FP.

The sensitivity and specificity of CBE was 94.59% and 90.47% respectively. The PPV 85.36%. The Error was 8% and Kappa statistic 0.832. Considering mammography, the sensitivity was 97.29% and specificity 93.65%. The PPV was 90%. Error was 5% and Kappa statistic 0.894. The sensitivity 97.29%, specificity 95.23%, PPV 92.30%, Error 4% and the Kappa statistic 0.915 were the statistics for FNAC. In the triple assessment, the sensitivity, specificity, PPV, NPV and accuracy were 97.29%, 98.41%, 97.29%, 98.41%, 98% respectively. The error was 2%. The Kappa statistic for the combination was 0.957. For triple test score, the sensitivity, specificity, PPV, NPV and accuracy were 100%, error was 0% and kappa statistic was 1 (Table 1).

Discussion

Breast lump is the clinical presentation of numerous breast disorders ranging from innocent benign cysts to malignant neoplastic lesions. Majority of breast symptoms or lesions will prove to be of a benign etiology. Distinction of benign from malignant is of paramount importance for patient care and proper management [2]. Physical, psychological and financial costs of investigating benign breast disease, primarily to exclude malignancy are substantial. Triple test was described initially in 1975. It refers to evaluation of palpable breast masses by clinical breast examination, mammography and fine needle aspiration cytology in women [2, 3].

Mokri M et al. [4] studied 100 cases of breast lump and they found sensitivity and specificity of 87% and 86% respectively (6 false positive, 8 false negative). Morris K T et al. [2] studied 484 palpable lesions and found 87% and 80% sensitivity and specificity respectively. Morris A et al. [3] had better sensitivity of 92% and lower specificity of 66.7% as compared to rest

Table 4: Triple test score

Clinical Breast Examination	Mammography	Fine needle aspiration cytology	Histopathological examination	Triple test score	Number of cases
Benign	Benign	Benign	Benign	3	51
Malignant	Malignant	Malignant	Malignant	9	31
Suspicious	Benign	Benign	Benign	4	5
Benign	Suspicious	Benign	Benign	4	4
Suspicious	Benign	Suspicious	Benign	5	1
Benign	Benign	Suspicious	Benign	4	2
Benign	Benign	Malignant	Malignant	5	1
Malignant	Malignant	Suspicious	Malignant	8	3
Malignant	Malignant	Benign	Malignant	7	1
Benign	Suspicious	Malignant	Malignant	6	1

Table 5: Comparison of statistical data with various previous studies

Authors	Clinical breast examination		Mammography		Fine Needle Aspiration Cytology		Triple Test		Triple Test Score	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specif
Morris KT *et al.* [2]	87	80	91	78	92	96	-	-	100	100
Morris A *et al.* [3]	92	66.7	96	66.7	96	100	100	57.1	100	100
Mokri M *et al.* [4]	87	86	93.5	79	89	90	-	-	98	100
Mulhim A S*et al.* [5]	82.6	97.3	87.5	97.3	91.7	100	-	-	100	100
Mande N *et al.* [6]	99.3	68.2	73.1	98.5	73.9	99.5	-	-	100	100
Sudarat N *et al.* [7]	-	-	-	-	92.5	90.2	-	-	-	-
Jensen A *et al.* [8]	-	-	-	-	-	-	99.1	100	-	-
Kaufman Z *et al.* [9]	89	60	89	73	93	97	100	57	-	-
Ahmed I *et al.* [10]	-	-	-	-	-	-	100	66.66	-	-
Present Study	94.59	90.47	97.29	93.65	97.29	95.23	97.29	98.41	100	100

of the studies. Study done by Al-Mulhim A S et al.[5] resulted in correct diagnosis by physical examination in 110 of 116 of benign cases, (specificity 97.3%, NPV 96.5%) with false positive results in 3 cases. A correct positive diagnosis was made by physical examination in 19 of 24 malignant cases, (sensitivity 82.6%, PPV 86.4%) with false negative in 4 cases. Mande N et al. [6] showed a sensitivity and specificity of CBE of 99.3% and 68.2% in his study. Present study showed sensitivity of 94.59% and specificity of 87.30% (8 false positive, 2 false negative) of clinical breast examination. (Table 5) The CBE was followed by mammography. Mammography was reported as per BIRADS classification. Different studies showed variable specificities for mammography. Mokri M et al. [4] showed sensitivity and specificity of 93.5% and 79% respectively while Morris K T et al. [2] showed 91% and 78% respectively and Morris A et al.[3]showed 96% and 66.7% respectively. Al-Mulhim A S et al. [5] study had 87.5% and 97.3% sensitivity and specificity respectively. Study done by Mande N et al. [6] had sensitivity and specificity of 73.1% and 98% respectively. Present study showed 97.29% and 93.65% of sensitivity and specificity respectively with 4 false positive and 1 false negative. The 4 false positive results were suspicious and on HPE were diagnosed as benign lesions. One false negative result was observed that was reported benign on mammography and on HPE confirmed to be malignant. (Table 5)

Most of the studies showed high sensitivity and specificity of FNAC which is consistent with present study. Morris A et al.[3]and Al-Mulhim A S et al.[5] both showed specificity of 100%. Al-Mulhim A S et al.[5], Sudarat N et al.[7] and Kaufman Z et al.[9] showed sensitivity of 91.7%, 92.5% and 93% respectively. Present study had sensitivity and specificity of 97.29% and 95.23% respectively. (Table 5). Jensen A et al. [8] in their nationwide study in Denmark had 99.1% and 100% sensitivity and specificity respectively for triple test. The present study had triple tests results nearly similar to this study with 97.29% sensitivity and 98.41% specificity. Rest of the studies by Morris A et al. [3], Kaufman Z et al. [9] and Ahmed I et al.[10] had low specificities of 57.1%, 57% and 66.66% respectively, while in all these studies the sensitivity was 100%. (Table 5).

Triple test score was compared with HPE in different studies. Morris K T et al. [2], Morris A et al.[3], Al-Mulhim A S et al.[5], Mande N et al.[6] showed 100% sensitivity, specificity, PPV and NPV. Present study also showed similar results for TTS with 100% sensitivity specificity, PPV and NPV. When TTS was less than or equal to 4 (n = 62) the specificity was 100%. When TTS was 6 or more than 6 (n = 36), sensitivity was 100%. There were two cases with TTS of 5, on HPE, one was benign and the other malignant.

Conclusion

Distinction of benign from malignant breast disease is of paramount importance for patient care and proper management. Triple test score is a powerful clinical tool that permits rapid, minimally invasive, cost-effective, easy to perform, time saving and accurate diagnosis of breast malignancies. In the present study, the accuracy was 100%. Management of diseases of the breast is a multidisciplinary endeavor dependent on the skill and expertise of an array of clinical specialists. "Triple Test Score" diagnosis service provides a reliable and accurate means of establishing a rapid diagnosis and is a safe and efficacious process for managing the ever-increasing number of patients presenting with breast masses. However, it can be applied only in those institutions where excellent imaging facilities as well as services of a cytopathologist are available.

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