Original Research Article

Predictability Score of Routine Screening Techniques and Triple Test in Diagnosis of Breast Lesions in a Tertiary Care Hospital

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ABSTRACT

Introduction: Increasing incidence of breast cancer, higher awareness in the society about this condition and easy availability of screening procedures has effected increased number of cases with breast-related symptoms for evaluation in clinical practice. Mammography and fine needle aspiration cytology are the main screening tests in evaluation of any breast lump. This study is carried out to compare the predictability of various breast lesions by individual screening test and by combined diagnostic approach utilizing Triple Test Score (TTS).

Aims and Objectives: The aim was to evaluate the role of TTS in palpable breast masses over individual screening test.

Materials and Methods: This prospective study was carried out from April 2015 to December 2016 in a tertiary care hospital in rural area as a combined effort involving the Departments of Pathology, Surgery and Radiology of a medical college. All cases were first evaluated clinically and then referred for mammography and FNAC of the breast mass, which were later diagnosed by histopathological examination. In the study period of 21 months, total 45 cases were studied where all three parameters of screening were utilized, i.e. clinical examination, mammography and FNAC followed by histopathological confirmation. TTS was then calculated in the evaluation of these lesions. The statistical parameters of sensitivity, specificity, Positive predictive value (PPV) and Negative predictive value (NPV) were calculated separately for malignant and non-malignant condition for each parameter of screening modality. Also a diagnosis match percentage was calculated for each parameter of screening modality, including TTS, irrespective of nature of disease (malignant or non-malignant) as per final histopathological diagnosis. This statistical data was compared to find out the better diagnostic modality of any breast lesion.

Results: Sensitivity, specificity, PPV and NPV was the best (>92%) irrespective of nature of the disease in TTS as compared to other screening modalities. Also the diagnosis match showed the best correlation with TTS (93.3%) than clinical (66.7%), radiological (51.1 %) or cytology (84.4%) score.

Conclusions: Triple test (TTS) is a very reliable method of evaluation for any palpable breast masses, whether benign or malignant, than utilizing fine needle aspiration cytology or mammography alone as a screening test. Histological correlation may be avoided before definitive treatment if Triple Test Score (TTS) is applied to all cases of breast lumps. However, it will require multiple as well as large scale studies from different part of the world to be implemented as a protocol for diagnosis and treatment.

Key words: *Breast lump, Bi-rad score, Mammographic screening, Fine needle aspiration cytology breast, Triple test, Triple test score*

INTRODUCTION

Breast related clinical conditions are very common in females of all age groups. [1] With increasing incidence and greater awareness of breast cancer, more patients present to the clinicians in the early stages of their disease. Self breast examination and screening mammography also detect many cases at earlier stages of disease. Hence the importance of screening tests increases in accurately diagnosing the lesion for appropriate treatment modality and better prognosis. [2] Though the incidence of neoplastic breast conditions is on rise, still wide array of non-neoplastic and benign conditions are more frequent in overall clinical presentation. This fact signifies the importance of basic screening investigations (e.g. Mammography and fine needle aspiration cytology) in diagnosis and treatment of various breast lesions including breast carcinoma. [3]

A combined diagnostic approach in diagnosing the condition will have advantage over single screening test. While mammography helps mainly in diagnosis of "in situ" carcinomas, it might fail to diagnose 10 % cases of malignancies in clinically detectable breast lumps. [4] Similarly, Fine Needle Aspiration Cytology will be more diagnostic in palpable breast lumps than in non-palpable breast conditions. The possibility of the diagnostic efficacy could further be enhanced when physical breast examination, mammography and FNAC (designated together as "Triple Test" [TT]) are jointly taken into consideration. Previous studies have found nearly 100% diagnostic accuracy of the TT for palpable breast masses when all three elements (i.e., physical examination, mammogram and FNAC) are concordant. A clinician can proceed directly with definitive therapy without an interventional open biopsy if all the components of TT are malignant. If all the components are found to be benign, the patient can then be safely observed. [5-8]

National Cancer Institute sponsored conference held in September, 1996, recommended a defined, uniform approach in breast FNAC and biopsy reporting to avoid controversies related to breast lump FNACs & core biopsies. These conference recommendations acknowledged the value of the "TT," in the reliable diagnosis of breast cancer. Consequently, it was suggested that a recommendation be included in the cytopathology reports of breast FNAs to support the clinical application of the "TT." [9] The present study is carried out to compare the predictability of various breast lesions by individual screening test and by combined diagnostic approach utilizing Triple Test Score (TTS).

Objectives:
1. To evaluate age wise prevalence, in our institute, of malignant versus non-malignant breast lesions.
2. To evaluate the efficacy of routine screening technologies in diagnosis of breast malignancy.
3. To determine predictability rate of Breast pathology by "Triple test score" over presently used screening tests.

MATERIALS AND METHODS

This prospective study was carried out at MVP's Dr. VPMC, Nashik, a tertiary care hospital in rural area over a period of 21 months from April 2015 to December 2016. The study was designed by the Department of Pathology and involved the Departments of Radiology and Surgery. All female patients coming with complaints of breast lump to the surgical out-patient department were clinically examined and a preliminary clinical score awarded. These patients were then advised mammography and FNAC followed by histopathological examination. Only the patients who consented for the above methodology were accepted. In the study period of 21 months total 45 cases were evaluated where all three parameters of screening were utilized, e.g. clinical history, mammography, FNAC and later histopathological confirmation. All

other cases which did not fulfill these criteria were excluded.

Prevalence of various breast lesions in two main categories i.e. Non-malignant and Malignant was calculated in two age groups i.e. cases below the age of 35 years and cases above the age of 35 years. Overall prevalence of Benign and Malignant lesions in these two age-groups was also calculated. The histopathological diagnosis was categorized into i) Malignant and, ii) Non-malignant lesion (which included benign tumors, inflammatory and other non-neoplastic disorders). This differentiation into malignant and non-malignant diseases was done, since we are always more concerned about early diagnosis, prognosis and treatment of malignant disease than that of non-malignant conditions. This prevalence data was calculated to nullify any age related bias in statistical parameters calculated in the below-mentioned scoring systems.

Each patient's clinical data, mammography findings and cytology data was analyzed and then converted into i) Clinical Score, ii) Radiology Score, and iii) Cytology Score for the calculation of TTS, as follows: [5]

Clinical Score:

On the basis of age of patient, clinical features of breast lump, its mobility, fixation to adjacent structures, associated changes in nipple, areola or skin and involvement of lymph nodes, a clinical suspicion of nature of lump is usually decided. Based upon these parameters, following clinical scores are recorded.
1. Definitely Benign
2. Suspicious for Malignancy
3. Definitely Malignant

Radiology Score: During mammography, the radiologist usually opines about breast lump in terms of BI-RADS (American College of Radiology; 2003; 4th Edition) score as follows:
- 0: Incomplete
- 1: Negative

- 2: Benign
- 3: Probably benign
- 4: Suspicious
- 4A: low suspicion for malignancy
- 4B: intermediate suspicion of malignancy
- 4C: moderate concern, but not classic for malignancy
- 5: Highly suggestive of malignancy
- 6: Known biopsy – proven malignancy

On the basis of BI-RADS score the Radiology Score is derived according to criteria laid by Morris et al (1998)[5] as follows:
1. Definitely Benign (BIRAD 0-2)
2. Suspicious for Malignancy (BIRAD 3-4)
3. Definitely Malignant (BIRAD 5-6)

Cytology Score: As per cytology smear diagnosis, the cytopathologist reports the breast lump FNAC in one of the following score –
1. Definitely Benign
2. Suspicious for Malignancy
3. Definitely Malignant

Triple Test Score (TTS) was calculated from addition of these scores (e.g. Clinical, Radiology and Cytology) for each patient and it was interpreted on a scale of 3 to 9 as follows: [5]
1. TTS <= 4 (3 or 4): Benign lesion
2. TTS = 5: Indeterminate lesion
3. TTS >= 6 (6,7,8 or 9): Malignant lesion

Match percentage was then calculated for each screening parameter against the final histopathological diagnosis of each patient as follows -
  a) Clinical Score against the histopathological diagnosis.
  b) Radiological score (initially expressed in Bi-RADS scoring system) and the histopathological diagnosis.
  c) Cytology score with the histopathological diagnosis.
  d) Triple Test Score (TTS) with histopathological diagnosis.

All this data was converted into Specificity, sensitivity, PPV (positive predictive value) and NPV (negative predictive value) of each screening parameter (e.g. Clinical, Radiological and Cytology as well as TTS) against the final histopathological diagnosis.

RESULTS

Amongst forty five cases in the study, the twenty three cases were below the age of 35 years while twenty two cases were of the age 35 years or above. As anticipated, 78.3 % cases in the age group below 35 years were finally diagnosed by histopathology to have benign (non-malignant) breast disorder while 21.7 % cases in group had malignant disease of breast. Group of cases with age 35 years and above had 13.6 % benign conditions and 86.4 % had malignant condition. The prevalence and type of breast pathology is categorized in the following table. (table-1)

Table : 1 : Age-wise distribution of breast lesions in Benign and malignant categories

	Below the Age of 35 Years	Above the Age of 35 Years
Benign Lesions	Fibroadenoma (N:16; 35.6 %)	Fibrocystic disease (N : 2; 4.4 %)
	Fibrocystic disease (N : 2; 4.4 %)	Phylloides tumor (N : 1; 2.2 %)
Total Benign Lesion percentage	(N:18; = 40 % of all cases studied; 78.3 % in cases below 35 years)	(N : 3; = 6.7 % of all cases studied; 13.6 % in cases above 35 years)
Total Malignant Lesion percentage	(N:5; =11.1 % of all cases studied; 21.7 % in cases below 35 years)	(N:19; = 42.2% of all cases studied; 86.4 % in cases above 35 years)
Malignant Lesions	Infiltrating Ductal Carcinoma (N : 5; 11.1 %)	Infiltrating Ductal Carcinoma (N : 18; 40 %)
		Cribriform carcinoma (N : 1; 2.2 %)

Benign disorders detected were Fibroadenoma (35.6 %), Fibrocystic disease of breast (8.8 %) and Benign Phylloides tumor (2.2 %). Malignant conditions diagnosed were infiltrating ductal carcinoma (51.1 %) and a case of Cribriform carcinoma (2.2 %). However, due to limited number of cases and due to selection criteria of the cases, these figures may not represent the real prevalence of these conditions.

Match percentage of each screening parameter (Clinical, Radiological, Cytological and TTS) was calculated on the basis of final histopathology diagnosis of every case. It is represented in table-2 as follows –

Table 2: Comparison of match percentage of individual screening modality against histopathological diagnosis

Test Parameter ➡ Statistical Parameter	Clinical Score	Radiology Score	Cytology Score	Triple Test Score
Match with Histopathology diagnosis (n/45)	30	23	38	42
Match with Histopathology diagnosis (%)	66.7	51.1	84.4	93.3
Unmatch with Histopathology diagnosis (n/45)	15	22	7	3
Unmatch with Histopathology diagnosis (%)	33.3	48.9	15.6	6.7

This table representing the "Match" percentage gives a better idea about accuracy of screening method in comparison to histopathological diagnosis. It shows the best match percentage (93.3 %) with TTS as compared to all other techniques used for breast lump screening. Match percentage is least (51.1 %) in the radiology screening method. Amongst the three cases which showed "Unmatch", two cases were reported as "Atypical ductal hyperplasia" in cytology, hence giving a lower cytology score. One case was initially suspected as fibrocystic disease, later found to be a case of focal infiltrating ductal carcinoma in histopathology.

Sensitivity, specificity, PPV and NPV was calculated for each screening method in comparison to histopathological diagnosis. These percentages are represented in Table. 3 as follows :-

Table 3: Sensitivity, specificity, PPV and NPV of each Screening method against Histopathology diagnosis

Test Parameter	Nature of disease (as per Histopathology Diagnosis)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Clinical Score	Malignant	43	90	83	59
	Non-malignant	90	84	59	84
Radiology Score	Malignant	81	73	75	79
	Non-malignant	70	85	82	74
Cytology Score	Malignant	88	100	100	86
	Non-malignant	100	88	86	100
Triple Test Score	Malignant	92	100	100	92
	Non-malignant	100	92	92	100

Sensitivity, specificity, PPV and NPV was the best (>92%) irrespective of nature of the disease in TTS as compared to other screening modalities. Cytology score was also a good screening method (>86% sensitivity, specificity, PPV & NPV) as compared to clinical or radiological score.

DISCUSSION

This study includes cases whose screening parameters like clinical suspicion, mammographic screening, FNAC of the breast lump as well as diagnostic parameter of histopathological evaluation of breast lump were done. It did not include the cases where any one of these screening or diagnostic parameters was not performed. Hence it excluded all cases without breast lump whose routine screening mammography was done without follow-up FNAC or biopsy. Similarly, it also excluded non-operable cases and cases where biopsy was not indicated. Hence, the prevalence data of this study will not indicate true prevalence of all the pathological lesions of breast. However, broadly the benign (non-malignant) lesions were common in cases with age less than 35 years and fibroadenoma was the most common benign disorder of breast in all age groups. Similarly, malignancy was more common in females of age group 35 years and above and the most common malignant condition was infiltrating ductal carcinoma.

Since the study included limited cases, the derived data was interpreted in terms of "Match" percentages of each modality of screening parameter against final, diagnostic histopathology report. According to the data presented in Table 2, the match percentage was best for "Triple Test Score" (93.3%) and least for Radiology score (51.1%). The percentage was fairly good for Cytology score (84.4 %), indicating the importance and reliability of cytology in the screening of breast lump. The low "Match" percentage of radiology score may be due to low reliability of BIRAD scoring in advanced malignant lesions with proximity to chest wall and extensive desmoplasia. Secondly, we are not considering a vast group of routine mammography screening cases, where radiology plays more important role than cytology for detection of "In-situ" malignancies. Thirdly, we have considered only BIRAD 5 & BIRAD 6 cases for Radiology score of 3. Hence, some highly suspicious cases like BIRAD 4 are considered as Radiology score as 2 and causes mismatch in the scoring.

The statistical parameters for the efficacy of the above screening methods were evaluated in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). As per the table 3, the cytology score and Triple test score (TTS) have maximum and almost similar values of sensitivity, specificity, PPV and NPV, though the values are marginally better for TTS. The specificity and PPV is the best (100 %) for malignant lesions for cytology score and TTS. However, sensitivity and NPV is the best (100 %) for non-malignant / benign lesions of breast by cytological screening and by TTS. Though, cytology has better sensitivity, specificity, NPV and PPV, it has few pitfalls in its reliability especially in case of focal lesions (e.g. malignancy), procedural failure, borderline results and certain gray zone lesions. Hence, the Triple

test score appears to be more apt screening parameter since it takes into consideration all screening aspects of breast lump like clinical evaluation, radiological and cytological screening.

The "Triple Test Score" (TTS) was initially described in the mid-1970s, by Johansen C. as the screening method of evaluation for palpable breast masses, which included the screening parameters like physical examination, mammography, and FNAC. Due to its technical simplicity, it has proved as a reliable tool for the accurate diagnosis of palpable breast masses. It has dual benefits of substantially reduced expense and morbidity as compared to open surgical biopsy. [5] Mammography is known to have reduced sensitivity and specificity of breast lesion detection in young women below 40 years of age, whereas sonography may be useful of in this group of patients. Hence the concept of "modified TTS" was introduced by the researchers, which is an integration of clinical breast examination, mammography combined with sonography and FNA while dealing with women under 40 years having palpable breast lump. [10] The TTS reliably guides evaluation and treatment of breast lesions. Lesions scoring 3 or 4 are always benign. Lesions with scores ≥6 are malignant and should be treated accordingly. Confirmatory biopsy is required only for the lesions that receive a TTS of 5. [11] Malignant lesion cases generally are not missed by TTS since it has 100 % specificity and PPV. As per present study, all cytological malignant cases showed TTS ≥6, except one case of IDC, where TTS was 5.

In the present study, TTS showed 93.3 % "match" with Histological diagnosis which correlates with studies by Ghafouri *et al* (94.38%), [10] Morris *et al* (92.12%) [5] and Hermansen *et al* (73.80%). [12] None of the benign cases in the present study showed discordant TTS which correlates with studies by Morris *et al* and Hermansen *et al*. Hence, the study suggests that TTS is a very good and reliable tool for diagnosis of breast lump with benign as well as

malignant lesions. Overall, TTS has good sensitivity, specificity, PPV and NPV. Although FNAC has long been indicated to be a good screening method for breast lump, [13] statistical analysis in the present study also indicates TTS to be a better tool than FNAC alone. If used judiciously, it may avoid many biopsy confirmations of breast lumps before definitive therapeutic strategy.

CONCLUSION

Triple test (TT) is a very reliable method of evaluation for any palpable breast masses, whether benign or malignant, than utilizing fine needle aspiration cytology or mammographic screening alone as a screening test. Histological correlation may be avoided before definitive treatment if Triple Test Score (TTS) is applied to all cases of breast lumps. However, it will require multiple as well as large scale studies from different part of the world to be implemented as a "protocol for diagnosis of any breast lump".

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