

PROSPECTIVE EVALUATION OF THE TRIPLE TEST FOR THE DIAGNOSIS OF PALPABLE BREAST MASS

AVALIAÇÃO PROSPECTIVA DO TESTE TRÍPLICE PARA O DIAGNÓSTICO DE NÓDULOS PALPÁVEIS DE MAMA

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ABSTRACT

Objective

To evaluate the validity of the triple test (clinical examination, mammography and fine-needle aspiration biopsy) in diagnosing palpable breast mass.

Methods

It was a prospective study for the validation of diagnostic tests, carried out at Center for Integral Assistance to Women's Health of the State University of Campinas. The participants were 102 women older than 30 years of age referred to a tertiary level hospital with palpable breast mass. The estimates of sensitivity, specificity and predictive values of the triple test were calculated using the histological evaluation of the lesions as the gold standard.

Results

The triple test presented sensitivity of 90%, specificity and positive predictive value of 100%, and negative predictive value of 82%. An evaluation of combinations of two tests was also performed, and the clinical examination with the fine-needle aspiration biopsy showed the best performance (sensitivity of 100% and specificity of 87%).

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Conclusion

The use of the triple test, especially when the results of the three tests are concordant, could decrease the number of surgeries in the case of benign diseases, and the number of complementary diagnostic procedures in the case of malignant diseases.

Index terms: breast neoplasms, mammography, fine-needle aspiration biopsy, clinical examination.

RESUMO

Objetivo

Avaliar a validade do teste tríplice (exame clínico, mamografia e punção aspirativa de agulha fina) no diagnóstico de nódulos mamários palpáveis.

Métodos

Este foi um estudo prospectivo de validação de testes diagnósticos, realizado no Centro de Atenção Integral à Saúde da Mulher da Universidade Estadual de Campinas. Participaram do estudo 102 mulheres com idade acima de 30 anos referidas para um centro hospitalar terciário com um nódulo mamário palpável. As estimativas de sensibilidade, especificidade e valores preditivos do teste tríplice foram calculadas usando o exame histológico das lesões como padrão ouro.

Resultados

O teste tríplice apresentou sensibilidade de 90%, especificidade e valor preditivo positivo de 100%, e valor preditivo negativo de 82%. Uma avaliação sobre as combinações de dois testes foi também realizada, e o exame clínico com a punção aspirativa de agulha fina mostrou o melhor desempenho (sensibilidade de 100% e especificidade de 87%).

Conclusão

O uso do teste tríplice, especialmente quando os resultados dos três testes isolados são concordantes, poderia diminuir o número de cirurgias no caso de doenças benignas e o número de procedimentos diagnósticos complementares no caso de doenças malignas.

Termos de indexação: *neoplasias mamárias, mamografia, punção aspirativa de agulha fina, exame clínico.*

INTRODUCTION

The appearance of a breast mass, noticed by the patient, continues being an important form of breast cancer presentation, mainly in developing countries. The majority of the cases of breast cancer diagnosed in these countries present that characteristic¹. In 2001, in Brazil, 31,590 new cases were diagnosed, representing the main death cause by malignant neoplasia among women².

In this country, due to little availability of resources for the performance of sophisticated diagnostic exams, the use of simple methods in a rational way becomes fundamental. These tests must, preferably, provide the accurate diagnosis of the disease, so that the appropriate treatment can be instituted.

The combined use of clinical examination, mammography and fine-needle aspiration biopsy, for the differential diagnosis of breast masses,

showed the viability and the superiority of the triple diagnosis, in comparison with the isolated use of these methods. Some studies confirmed that the combined utilisation of tests, used for the diagnosis of palpable breast mass, showed high accuracy, especially in the cases of breast cancer³⁻⁷. The best results were found when the three tests were concordant⁸.

The present study aimed to evaluate the performance of the combined use of clinical examination, mammography and fine-needle aspiration biopsy (the triple test), in the diagnosis of palpable breast lumps in women over 30 years of age.

METHODS

This was a prospective study to evaluate the validity of diagnostic tests, by calculating the sensitivity, the specificity and the positive and negative predictive values of the triple test (clinical examination, mammography and fine-needle aspiration biopsy). Different combinations of two tests were also analysed. The gold standard, performed in all the cases, was the histological evaluation of the breast masses.

The calculated sample size was 96 women, considering a proportion of true positive for malignancy of 90%, a maximum desired difference between the proportions of sample and population of 6%, and an alpha error of 5%. The data collection period was from January 1996 to July 1998 at a tertiary level hospital (CAISM – Center for Integral Assistance to Women's Health) of the State University of Campinas, in the state of São Paulo, Brazil, where all cases were referred to. The information available at the end of the study was of 102 cases, and that was used in the analysis.

The women included in this study were 30 years or older, presented palpable breast mass at the physical examination, and had undergone all tests. The women with previous malignant

homolateral breast neoplasia and cysts, diagnosed by fine-needle aspiration, were excluded from the research.

Clinical examination was performed by a sole physician, the principal investigator, during the first visit, and it started with the anamnesis, followed by the physical examination. This consisted of static and dynamic inspections, and of palpation of the breast and axilla.

A specially trained physician and also a radiologist separately evaluated the mammography of each breast performed in two views (craniocaudal and mediolateral), with complementary projections in some cases. Their findings were only based on the evaluation of the X-rays, taking into account the examiner was blinded to the data of the patients' clinical examination.

The same examiner also performed all fine-needle aspiration biopsies. For that, metallic handlings were used, as well as disposable syringes and needles. Four slides were taken, on the average, by lump. The slides were evaluated by the cytologists of the institution. In the cases where the results of the slides were insufficient or unsatisfactory, a second biopsy was accomplished.

Histological evaluation was performed, in each case, after surgical or core-needle aspiration biopsies (four cases), and the reports were issued by pathologists.

The results of the clinical examination and of the mammography were classified as benign or probably benign and malignant or probably malignant. The results of the aspiration biopsies were classified as benign, suspected/malignant or insufficient/unsatisfactory (not included in the calculation of the fine-needle aspiration accuracy, and placed in the discordant triple test group). The cases were classified by histological evaluation as benign or malignant.

The Student's "t" test was used for calculating the statistical significance of the

differences found in the analysis of age and mass diameter in the two groups (malignant or benign disease). The sensitivity, the specificity and the positive and negative predictive values of the triple test were calculated, in different combinations of two tests, of at least two positive tests or at least a positive one. The statistical package Epi Info version 6.02 was used for the procedures of statistical analysis. The research project was previously approved by the Research Committee and by the Research Ethics Committee of the institution.

RESULTS

Of the 102 women evaluated in this study, 69% experienced malignant diseases, and 31%, benign ones. All women were older than 30 years of age, with a mean of 53.4 years. In the malignant disease group, the mean age was significantly higher than the one of the benign disease group. The mean diameter of the breast lumps in mammography was 2.56cm. The mean diameters of both groups were similar (Table 1).

In the isolated evaluation of the three tests, the clinical examination had a sensitivity of

93%, a specificity of 94%, a positive predictive value of 97% and a negative predictive value of 86%. The mammography showed a sensitivity of 96%, a specificity of 69%, a positive predictive value of 87% and a negative predictive value of 88%. The fine-needle aspiration biopsy had a sensitivity of 97%, a specificity of 87%, a positive predictive value of 94% and a negative predictive value of 93% (Table 2).

The results of the three tests were concordant in 79% of the cases, with all the outcomes either positive or negative. In 21% of the cases the results of the tests were discordant.

The findings of the triple test were classified as malignant when the three exams showed malignant diseases, and benign when benign diseases were shown in the three procedures or in case of disagreement among the test diagnoses. Therefore, it had a specificity of 100% and a sensitivity of 90%. The positive predictive value demonstrated that in all cases with triple test positive for malignancy the histological evaluation revealed malignant neoplasia. The negative predictive value was 82% (Table 3).

Table 1. Age of the women and tumor diameter in the groups with malignant or benign breast diseases.

Disease	Age (years)			<i>p</i>	Diameter of tumor (cm)		
	n	Mean	SD		Mean	SD	<i>p</i>
Malignant	70	55.6	11.8	0.006	2.49	0.71	NS
Benign	32	48.7	10.6		2.72	1.52	
Total	102	53.4	11.8		2.56	2.56	

Table 2. Sensitivity, specificity, positive predictive value and negative predictive value of isolated tests for breast mass malignancy (%).

Test	Sensitivity	Specificity	PPV	NPV
Clinical	93	94	97	86
Mammography	96	69	87	88
ENA*	97	87	94	93

(*) FNA - fine-needle aspiration.

When the accuracy of the combined diagnoses was evaluated considering at least one of the three tests positive for malignancy in only one of the malignant cases none of the tests were positive (benign clinical exam and mammography, aspiration biopsies with insufficient material). However, the specificity in that situation dropped to 56% (Table 4).

In the analysis of the performance of breast cancer diagnoses considering at least two tests positive for malignancy, the sensitivity decreased (96%), and the specificity improved (94%) (Table 5).

Table 3. Performance of the triple test in diagnosing breast mass malignancy.

Triple test	Histology		n
	Malignant	Benign	
Malignant	63	0	63
Benign	7	32	39
Total	70	32	102

Sensitivity = 90% Specificity = 100%
Positive predictive value = 100%; Negative predictive value = 82%.

Table 4. Performance of the breast malignant tumor diagnosis, considering at least one of the three tests positive for malignancy.

Combined results	Histology		n
	Malignant	Benign	
At least one of the tests positive	69	14	83
No positive test	1	18	19
Total	70	32	102

Sensitivity = 99% Specificity = 56%
Positive predictive value = 83%; Negative predictive value = 95%.

Table 5. Performance of breast malignant tumor diagnosis, considering at least two tests positive for malignancy.

Combined results	Histology		n
	Malignant	Benign	
At least two positive tests	67	2	69
Only one or no positive tests	3	30	33
Total	70	32	102

Sensitivity = 96% Specificity = 94%
Positive predictive value = 97%; Negative predictive value = 91%.

In the analysis including only the three concordant tests, in spite of being partial, the sensitivity, the specificity and the positive and negative predictive values would be 100%, with an accurate diagnosis in all the cases. However, according to the histology, seven malignant tumors and fourteen benign ones were excluded from this analysis.

In the group with discordant results of the three tests, the majority was of women with benign diseases (67%). The mean mass diameter in this group was 2.29cm, slightly below the general mean (2.56cm). The mean age was 51.5 years. The disease producing more discordance in the tests was the fibroadenoma (29% of the cases), and the ductal invasive carcinoma (four cases) was in the second place. An analysis of the sensitivity and specificity of combinations of two tests was performed, and the three combinations of the two tests presented high sensitivity. However, the clinical examination with the fine-needle aspiration showed the best specificity (Table 6).

Table 6. Sensitivity and specificity of different combinations of two tests for the diagnosis of breast mass malignancy.

Combination of two tests	Sensitivity	Specificity
Clinical exam + mammography	97	63
Clinical exam + FNA*	100	87
Mammography + FNA*	99	58

(*) FNA - fine-needle aspiration.

DISCUSSION

The results of this study showed that the triple test presented the maximum positive predictive value in diagnosing cancer in women with palpable breast mass. Therefore, all cases with the three procedures indicating malignant disease were confirmed with the histology of the lesion. This test demonstrated high sensitivity, and a specificity of 100%, confirming its high capacity to discard malignancy. This method

has also shown a satisfactory negative predictive value.

In this research, the triple test was considered positive when the three exams indicated malignancy, and negative in other situations (when all the tests indicated benign results or when there was disagreement among the results of the exams). The findings were comparable or even superior to the ones of other studies that performed similar analysis^{5,6}.

Other authors, however, considered the triple test positive when at least one of the tests was positive for malignant disease, reaching an excellent sensitivity, but with a much smaller specificity⁴. Their results were also similar to the ones of this study.

Another type of triple test analysis can be made, considering it positive when the three exams indicate malignant disease, and negative when all indicate benign disease. In this situation, the cases in which the tests are discordant are not considered, leading to a partial and tendentious analysis of the results. The studies that followed this idea found an almost perfect performance of the triple test^{5,9}, which would be confirmed in this research. This would be the ideal situation for its practical use; however, it is worthwhile to remember that the percentage of cases with discordant results can represent a significant number of the total. In the present study this percentage was 21%, inferior to the ones of the other authors^{5,6,9}.

Few studies have analysed different combinations of two tests with the same results. When the combination of clinical examination and mammography was evaluated, a sensitivity similar and a specificity inferior to the ones of other authors were found^{6,10}. In this research, the best combination of two tests was the clinical examination with the fine-needle aspiration biopsy, which was different from other authors who indicated the best combination was the mammography with the fine-needle aspiration⁵. This kind of evaluation can help the cases in

which the results of all tests are not concordant, and this situation can be frequent. Fine-needle aspiration biopsy is the test with the highest isolated value and it should, whenever possible, direct the conduct in the discordant cases¹¹⁻¹⁵.

The findings of this study indicate that the best performance of the triple test is obtained when the three exams are concordant, for malignant or benign diseases. The concordant triple test used in the diagnosis of palpable breast masses can reach sensitivity similar to the one of the frozen biopsy, with comparable false-positive results¹⁶⁻¹⁹. The false-negative results of the concordant triple test can have a percentage very close to the one of the conventional surgical biopsy¹⁷.

A study showed also that, when the surgical biopsy for diagnosis confirmation of palpable breast mass is only accomplished in the cases with discordant test results, the total number of surgeries can be cut in half, representing a great reduction in costs⁵.

CONCLUSION

Management based on the triple test could be proposed, taking into account the present results, in addition to other findings derived from this study and previously reported^{20,21}. When the triple test is concordant in a benign case, a periodic clinical and image control of the cases can be indicated, besides guiding the patient to perform a monthly breast self-examination. The concordant triple test for malignancy will allow the accomplishment for the definitive treatment for the disease, without obligating the performance of a pre or an intraoperative histological evaluation.

Among developing countries, these facts can help diminish the indication of surgeries for benign diseases and discard other diagnostic methods in the malignant cases, as the core-needle aspiration and the frozen biopsies, thus

reducing costs. It is important to remember that attention is fundamental in the isolated performance of the tests. The tests technique should be carefully followed and their results should be independent of knowledge of clinical conditions, in order to achieve satisfactory outcomes.

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