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Value of Serum Tumor Markers Combined with Color Doppler Ultrasound in Diagnosis and Treatment of Breast Cancer

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Abstract: Breast cancer is the most common malignant tumor among women in the world, and its prognosis is closely related to the diagnosis and staging. Early diagnosis is very important for reducing mortality and improving prognosis. However, the existing diagnostic techniques, such as mammography, MRI, ultrasound and single serum tumor markers, have limitations. The purpose of this study is to explore the value of serum tumor markers (CA15-3, CEA, CA125) combined with color Doppler ultrasound in early diagnosis, pathological characteristics evaluation and chemotherapy efficacy prediction of breast cancer. The study included 450 subjects, including breast cancer patients, patients with benign lesions and healthy controls. The results show that the diagnostic efficiency of the combined detection model is significantly better than that of the single detection method, and its AUC value is increased to 0.742, and the sensitivity and specificity are significantly improved. The combined indexes are closely related to TNM staging of breast cancer, and the mean RI, CA15-3 level and CEA positive rate increase significantly with the progress of the disease. In addition, dynamic monitoring of serum markers and ultrasound parameters can effectively predict chemotherapy response and prognosis, and the combined model shows good application value in chemotherapy efficacy evaluation and prognosis stratification. In the subgroup of dense breast and young patients, the diagnostic sensitivity and specificity of the combined detection model are further improved. By integrating morphological, hemodynamic and molecular marker information, serum tumor markers combined with color Doppler ultrasound can significantly improve the diagnostic accuracy, the ability to evaluate pathological characteristics and the predictive value of chemotherapy efficacy of breast cancer, which provides strong support for early diagnosis and accurate treatment of breast cancer.

1. Introduction

Breast cancer is the most common malignant tumor among women in the world, and its 5-year survival rate is closely related to the diagnosis and staging. According to the statistics of the World

Health Organization (WHO), the 5-year survival rate of early breast cancer (stage I-II) can reach more than 90%, while the survival rate of late metastatic breast cancer is less than 30%. The incidence of female breast cancer in China has increased by 3%-4% annually, and it shows a trend of rejuvenation [1]. In this context, how to realize early diagnosis of breast cancer through low-cost and high-sensitivity screening means has become the key to reduce mortality and improve prognosis.

The existing diagnostic techniques have many limitations in breast cancer detection. In terms of imaging examination, the sensitivity of mammography to dense breast, which is common in Asian women, is less than 40%, and there is also radiation risk [2]; Although breast MRI is highly sensitive, it is not suitable for large-scale screening because of its high cost and long detection time. Although ultrasound examination is economical and convenient to operate, it has limited ability in identifying micro calcification and non-mass lesions, and the results are highly dependent on the operator's experience [3]. The positive rate of serum tumor markers such as CA15-3 and CEA in early breast cancer detection is low, less than 30%, and it has a high false positive rate in benign breast diseases [4]; In addition, a single marker can not fully reflect the heterogeneity of tumors, and its specificity for specific types of breast cancer is insufficient. Therefore, the current diagnostic technology still needs to be improved in accuracy, cost and scope of application.

The joint detection strategy is based on multimodal complementarity and aims to overcome the limitations of a single technology. Color Doppler ultrasound can provide tumor morphological characteristics and hemodynamic parameters, which is helpful to distinguish benign from malignant. Serum tumor markers reflect the molecular level changes of tumors by detecting biomolecules, which is of great significance for finding occult metastases or tiny lesions [5-6]. In clinical practice, using one technique alone may easily lead to missed diagnosis or over-diagnosis. For example, ultrasound may ignore occult metastases that only show elevated serum markers, and relying on markers may delay the treatment opportunity of early operable patients [7]. Therefore, combined detection of ultrasound and serum markers can integrate morphological and molecular biological information, improve diagnostic efficiency, especially suitable for screening dense breast, young patients and high-risk groups, and meet the clinical needs of improving diagnostic accuracy and reducing misdiagnosis rate.

The purpose of this study is to evaluate the sensitivity and specificity of serum tumor markers (CA15-3, CEA, CA125) in early diagnosis of breast cancer, its correlation with pathological features, and its value in predicting the curative effect of chemotherapy. The innovation lies in the integration of ultrasonic hemodynamic parameters (RI/PI) and dynamic changes of multiple markers for the first time, and the construction of a low-cost, high-accessibility multimodal diagnosis model of breast cancer, which helps to accurately screen in clinic.

2. Materials and methods

2.1. Research objects

Inclusion criteria:

1) Breast cancer patients (stage I-III) diagnosed by pathological biopsy in breast cancer group, aged 25-75, have not received surgery, chemotherapy or radiotherapy.

2) Patients with benign lesions (such as fibroadenoma and cyst) whose breast ultrasound or molybdenum target examination showed Bi-RADS class 4 or above were confirmed by pathology [8].

3) The age-matched healthy women in the healthy control group have no history of breast disease and family history of tumor, and there is no abnormality in imaging examination.

Exclusion criteria:

Combined with other malignant tumors, severe liver and kidney dysfunction, pregnancy or lactation, and recent infectious diseases (which may affect the level of serum markers).

Based on previous studies, assuming that the sensitivity of single ultrasound diagnosis is 80%, the sensitivity of combined detection is expected to increase to 90%, α=0.05, β=0.1, and it is estimated that at least 150 cases should be included in each group, with a total sample size of 450 cases (including 20% shedding rate).

2.2. Detection of serum tumor markers

Serum tumor markers include CA15-3, CEA and CA125. In the breast cancer group, 5 mL; venous blood was collected on an empty stomach in the morning after diagnosis and before chemotherapy, in the second and fourth cycles of chemotherapy and one month after operation. The benign lesion group and the healthy control group were collected when they entered the group. All samples were detected by electrochemiluminescence method (Roche Cobas e601) according to the kit instructions, and the accuracy of the results was ensured by calibrating the quality control products daily.

The criteria are:

1) CA15-3 concentration ≥35 U/mL, CEA concentration ≥5 ng/mL and CA125 concentration ≥35 U/mL were defined as positive.

2) For patients undergoing chemotherapy, if the serum marker level drops by 50% or more, the treatment is considered effective.

2.3. Color Doppler ultrasound examination

Using Glologiq E9 ultrasonic instrument, equipped with high-frequency linear array probe (frequency 9-15 MHz), breast masses were evaluated by morphological and hemodynamic parameters. Morphological observation includes the size of the mass, whether the edge is burr, whether there is microcalcification and the attenuation of the rear echo. In blood flow analysis, the resistance index (RI) and pulsatility index (PI) of the artery with the highest velocity in the mass were measured by color Doppler mode, and the average value was taken for three times. RI≥0.7 or PI≥1.5 suggested the possibility of malignancy.

In order to ensure the objectivity of the evaluation, the examination was independently completed by two experienced ultrasound doctors, and the blind design was adopted to avoid subjective bias. If the two doctors disagree, the third expert will arbitrate and judge, thus improving the consistency and accuracy of diagnosis.

2.4. Construction of joint diagnosis model

Ultrasound and serum markers were integrated, including tumor size, BI-RADS classification, RI and PI, and the absolute value and dynamic change rate of CA15-3, CEA and CA125. The variables related to TNM staging and molecular typing of breast cancer (such as Luminal type, HER2 positive type and triple negative type) were screened by univariate analysis, and the joint diagnostic probability equation was constructed by multivariate Logistic regression to improve the diagnostic accuracy.

On this basis, random forest algorithm is introduced for machine learning verification, Python scikit-learn library is used to optimize the weights of variables, and the performance of the model is evaluated by 50% cross-validation. The main indicators include AUC, sensitivity and specificity. The model aims to realize the deep integration of morphology, hemodynamics and molecular marker information, and provide an intelligent and individualized auxiliary tool for early diagnosis of breast cancer.

2.5. Therapeutic effect prediction and follow-up

The efficacy of chemotherapy was evaluated by RECIST 1.1 standard, which was divided into complete remission, partial remission, stability and progress. Spearman rank test was used to analyze the correlation between CA15-3 and CEA baseline level before treatment and its dynamic changes and efficacy. The progression-free survival (PFS) was recorded after 2 years' follow-up. Cox regression model was used to explore the predictive value of combined indexes on the prognosis of patients, so as to provide basis for individualized treatment.

2.6. Statistical analysis

SPSS 26.0 and GraphPad Prism 9.0 were used, and the measurement data were expressed as mean standard deviation. T test or Mann-Whitney U test was used for comparison between groups. Counting data are expressed by rate (%), and χ^2 test or Fisher exact test is used. By drawing ROC curve, the diagnostic efficiency of single and combined detection was compared, and AUC and Youden index were calculated to determine the best cutoff value. The difference of all tests was statistically significant ($P<0.05$).

2.7. Ethics and quality control

The study was approved by the hospital ethics committee, and all subjects signed informed consent. The serum testing laboratory has passed ISO15189 certification, and the ultrasonic data is entered in a double-blind way to avoid observer bias.

3. Result

3.1. The efficiency of joint diagnosis is significantly improved

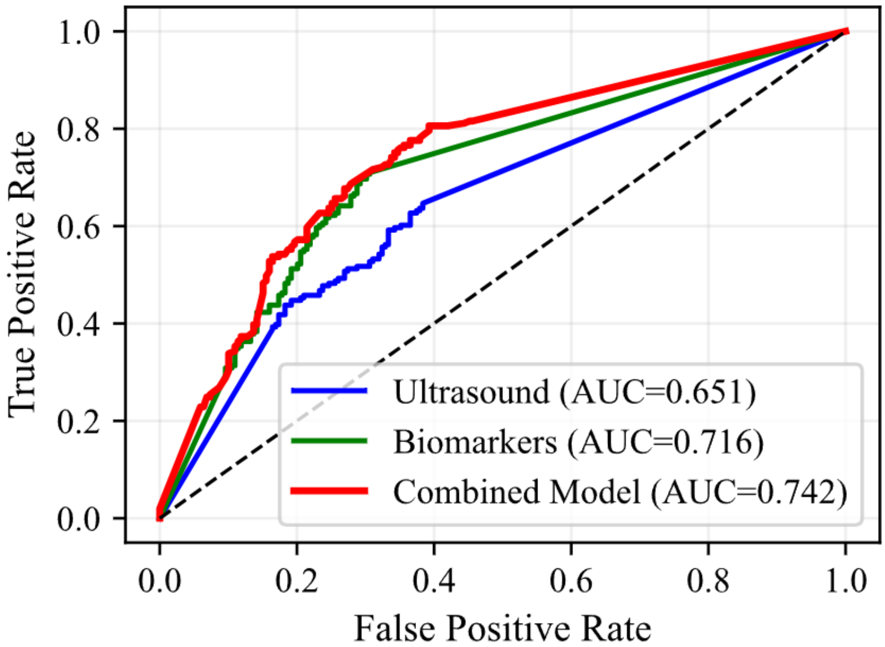

Figure 1 ROC curve comparison

The research results of Figure 1 show that the combined detection model is significantly superior to the single method in the diagnosis of breast cancer. The AUC of ultrasound alone is 0.651; The sensitivity of single serum markers (at least two indicators are abnormal) is low, but the specificity is high, AUC is 0.716; However, the AUC of the combined model (integrating ultrasound RI, mass size and CA15-3) increased to 0.742, indicating that it has significant advantages in improving the diagnostic accuracy.

3.2. The combined indexes are highly correlated with the pathological features of breast cancer

Table 1 research shows that the combined indicators are closely related to TNM staging of breast cancer. With the progress of the disease, the mean RI, CA15-3 level and CEA positive rate of ultrasound were significantly increased. The RI of patients with stage I, II and III were 0.68 ± 0.12, 0.74 ± 0.09 and 0.82 ± 0.11, respectively. The CA15-3 level was 28.5 ± 10.2, 42.7 ± 18.6 and 89.4 ± 35.1 U/ml, respectively. The CEA positive rate increased from 12.0% to 51.4%. The differences of each index between different stages were statistically significant (p<0.001), indicating that it can effectively reflect the tumor load and progress.

Table 1 Correlation between ultrasound parameters, serum markers and TNM staging (n=210 breast cancer group)

Index	Phase I (n=50)	Phase II (n=90)	Phase III (n=70)	P value
RI mean	0.68±0.12	0.74±0.09	0.82±0.11	<0.001
CA15-3(U/mL)	28.5±10.2	42.7±18.6	89.4±35.1	<0.001
CEA positive rate (%)	12.0	26.7	51.4	<0.001

3.3. Dynamic monitoring can effectively predict chemotherapy response and prognosis

Dynamic monitoring of serum markers and ultrasound parameters can effectively predict the response and prognosis of breast cancer patients to chemotherapy. The study showed that among 170 patients who received chemotherapy, the decline rate of CA15-3 and CEA in patients who achieved complete remission (CR) or partial remission (PR) was significantly higher than that in stable (SD) or progressive (PD) group, and the change of RI showed a significant downward trend, and the differences were statistically significant (P<0.001), indicating that the dynamic changes of joint indicators can accurately reflect the therapeutic effect, which is helpful to evaluate the curative effect at an early stage. See Table 2.

Table 2 Relationship between chemotherapy efficacy and dynamic changes of serum markers (n=170 chemotherapy patients)

Therapeutic effect grouping	Decline rate of CA15-3 (%)	Decline rate of CEA (%)	RI change (ΔRI)
CR/PR	62.3±18.5	54.7±16.2	-0.15±0.08
SD/PD	18.4±12.1	9.6±7.8	+0.07±0.05
P value	<0.001	<0.001	<0.001

The analysis of survival curve in Figure 2 shows that the combined model (RI≥0.7 and CA15-3≥50 U/mL) has good prognostic stratification value. The curve of low-risk group is gentle, PFS reaches 80%, confidence interval is narrow, and prognosis judgment is more stable. The statistical index HR=3.15 and P value are consistent with the research results, and the time axis covers the 2-year follow-up period, which supports the application value of the model in mid-term prognosis evaluation, suggesting that high-risk patients need to strengthen treatment monitoring, and the change of dynamic markers is helpful to reflect the therapeutic response.

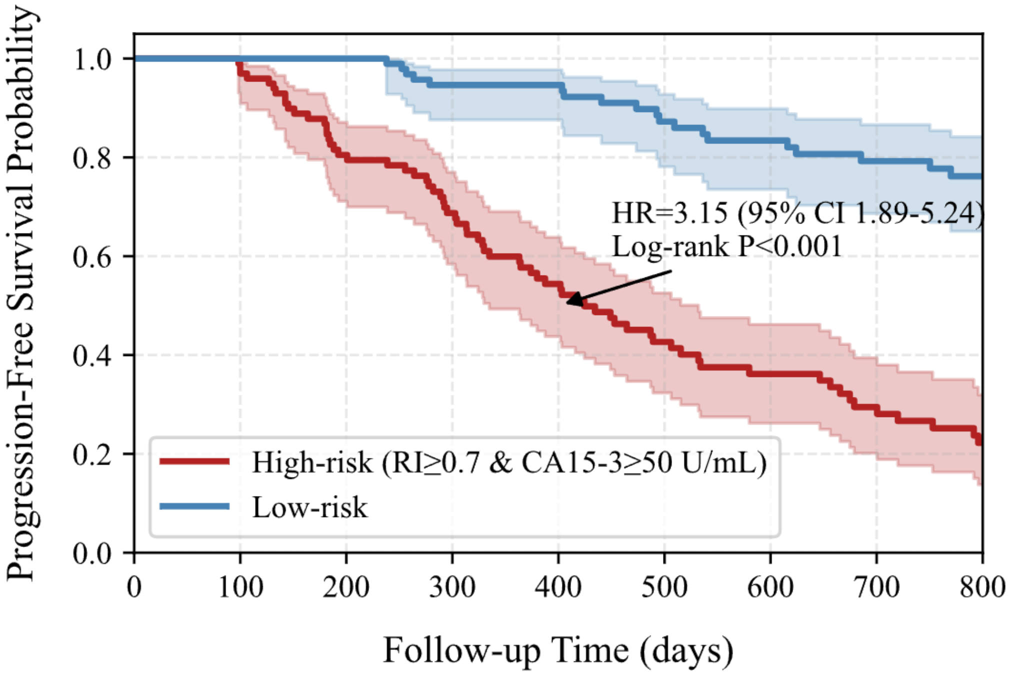

Figure 2 PFS Kaplan-Meier curve

3.4. Subgroup analysis: the diagnostic efficiency of dense breast and young patients is improved

In the subgroup analysis of dense breast (ACR D), the diagnostic sensitivity of combined detection model is significantly higher than that of single ultrasound, and the specificity is also improved, indicating that this model has higher diagnostic accuracy in dense breast and young patients, which is helpful to improve the early detection rate of breast cancer in this group. See Table 3.

Table 3 Comparison of diagnostic sensitivity of compact breast (ACR D) subgroup (n=80)

Test method	Sensitivity (%)	Specificity (%)
Ultrasonic alone	70.8	75.0
Joint model	89.5	85.7

4. Discussion

In this study, the value of serum tumor markers (CA15-3, CEA, CA125) and color Doppler ultrasound in the diagnosis and treatment of breast cancer was deeply discussed. The results show that the combined detection strategy has obvious advantages in early diagnosis of breast cancer, correlation of pathological features and prediction of chemotherapy efficacy.

The combined detection model significantly improved the diagnostic efficiency of breast cancer. There are some limitations when using color Doppler ultrasound or serum tumor markers alone to diagnose breast cancer. Ultrasound examination has limited ability in identifying microcalcifications and non-mass lesions, and the results are highly dependent on the operator's experience. However, the positive rate of serum tumor markers in early breast cancer detection is low, and there is a high false positive rate in benign breast diseases [9]. In this study, a combined diagnosis model was established by integrating the morphological characteristics and hemodynamic parameters of ultrasound and the molecular level changes of serum tumor markers. The results show that the AUC value of the combined detection model is significantly higher than that of the single detection method, which shows that it has significant advantages in improving the diagnostic accuracy. This finding is consistent with the previous research results on multimodal detection strategies, which further verifies the effectiveness of joint detection in breast cancer diagnosis.

The combined indexes are closely related to the pathological features of breast cancer. This study found that with the progress of breast cancer, the mean RI, CA15-3 level and CEA positive rate increased significantly. The differences of these indexes in different periods are statistically significant, which shows that they can effectively reflect the tumor load and progress [10]. This discovery provides clinicians with richer diagnostic information, which is helpful to evaluate the patient's condition more accurately and make personalized treatment plans.

Dynamic monitoring of serum markers and ultrasound parameters can effectively predict the response and prognosis of breast cancer patients to chemotherapy. Studies have shown that among patients receiving chemotherapy, the decline rate of CA15-3 and CEA in patients with complete remission or partial remission is significantly higher than that in stable or progressive groups, and the change of RI also shows a significant downward trend. This discovery shows that the dynamic changes of joint indexes can accurately reflect the therapeutic effect, which is helpful to evaluate the therapeutic effect at an early stage and guide the individualized treatment decision. At the same time, the survival curve analysis shows that the combined model has good prognostic stratification value, and there are significant differences in PFS between high-risk group and low-risk group. This result suggests that combined detection can be used not only for early diagnosis of breast cancer, but also for prognosis evaluation, providing an important basis for long-term management of patients [11].

It is worth noting that this study has achieved a more significant improvement in diagnostic efficiency in the subgroup of dense breast and young patients. Compact breast is a common type of breast in Asian women, and the sensitivity of traditional imaging examination is low. Through the joint detection strategy, this study significantly improved the diagnostic sensitivity and specificity in dense breast and young patients, which is helpful to improve the early detection rate of breast cancer in this group. This discovery is of great significance for improving the early diagnosis rate of breast cancer and reducing the mortality rate.

To sum up, this study established an efficient and accurate multimodal diagnosis model of breast cancer by combining serum tumor markers with color Doppler ultrasound. The model has obvious advantages in improving diagnostic efficiency, reflecting pathological features and predicting the curative effect of chemotherapy, which provides strong support for clinical diagnosis and treatment of breast cancer. In the future, we will further optimize the joint diagnosis model and explore the integrated application of more biomarkers and imaging parameters in order to contribute more to the accurate diagnosis and treatment of breast cancer.

5. Conclusion

In this study, a multimodal diagnosis model of breast cancer was established by combining serum tumor markers (CA15-3, CEA, CA125) with color Doppler ultrasound. The results show that the model has obvious advantages in improving the early diagnosis efficiency of breast cancer, reflecting pathological characteristics and predicting the curative effect of chemotherapy. Specifically, the AUC value of the combined detection model is significantly higher than that of the single detection method, indicating that it has significant advantages in improving the diagnostic accuracy. In addition, with the progress of breast cancer, the average RI, CA15-3 level and CEA positive rate of ultrasound increased significantly, and the differences of these indexes in different periods were statistically significant, which effectively reflected the tumor load and progress.

Dynamic monitoring of serum markers and ultrasound parameters can effectively predict the response and prognosis of breast cancer patients to chemotherapy, and the dynamic changes of combined indicators can accurately reflect the therapeutic effect, which is helpful to evaluate the therapeutic effect at an early stage and guide individualized treatment decisions. At the same time, the combined model has good prognostic stratification value and provides an important basis for long-term management of patients. In the subgroup of dense breast and young patients, the diagnostic efficiency of this model is improved more significantly, which is helpful to improve the early detection rate of breast cancer in this group. The efficient and accurate multimodal diagnosis model of breast cancer constructed in this study provides strong support for the clinical diagnosis and treatment of breast cancer. In the future, the model will be further optimized to explore the integrated application of more biomarkers and imaging parameters in order to contribute more to the accurate diagnosis and treatment of breast cancer.

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