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ORIGINAL ARTICLE

Value of tissue elastography in the prediction of efficacy of neoadjuvant chemotherapy in breast cancer

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Summary

Purpose: *The purpose of the present study was to explore the value of real-time tissue elastography (RTE) in predicting the efficacy of neoadjuvant chemotherapy (NAC) in breast cancer.*

Methods: *A total of 60 patients with breast cancer who received NAC in our hospital were evaluated. According to the pathological results, 47 patients were included in the significant response group and 13 patients in the non-significant response group. The maximum diameter and strain ratio (B/A ratio) of lesions before and 1st, 2nd, 4th and 6th week after NAC were recorded and compared. The receiver operation characteristics (ROC) curve of the lesion diameter and strain rate ratio (B/A value) were used to predict the value of NAC efficacy.*

Results: *The lesions in the two groups showed a honeycomb-like reduction after NAC. The blue color in the elastic image gradually decreased, and the green color gradually increased. Repeated analyses of variance (ANOVA) found that the maximum diameter and B/A value showed a downward trend within 6 weeks of NAC treatment. The maximum diameter and B/A value in the significant response group were significantly lower than the non-significant response group before and after the NAC. There was an interaction in the maximum diameter and B/A value between the significant response group and the non-significant response group. The above differences were statistically significant (all $p<0.05$). The area under the curve (AUC) of ΔB/A value at 2nd week of NAC was maximal (0.944), and the best diagnostic point was 5.64. The sensitivity was 92.31% and the specificity 87.23%.*

Conclusions: *ΔB/A value at 2nd week of NAC is helpful in predicting the therapeutic effect of NAC in breast cancer.*

Key words: *breast cancer, neoadjuvant chemotherapy, real-time tissue elastography, strain ratio*

Introduction

Neoadjuvant chemotherapy (NAC) is applied to patients with locally advanced breast cancer, patients with inflammatory breast cancer, and patients who wish to retain the breast but have a larger lesion [1]. Effective evaluation of its early efficacy is helpful in the follow-up treatment. The clinical methods of NAC efficacy evaluation include palpation, mammography, and ultrasound. However, these methods are not effective in evaluating the efficacy of NAC due to the honeycomb-like reduction in lesion after NAC. The boundary of lesion is difficult to define [2,3]. As an imaging tool for observing the tissue hardness, ultrasound elastography has been widely used in the evaluation of benign and malignant tumors [4,5]. The study by Sahoo et al. [6] found that the hardness of the lesions changed after NAC. Hence, elastography may be an effective method for NAC evaluation. The aim of the present study was to evaluate the value of NAC efficacy based on elastography. This study is expected to help the treatment of breast cancer.

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Methods

Subjects of the study

Breast cancer patients who received NAC in our hospital from February 2016 to February 2018 were enrolled as research subjects. *Inclusion criteria:* 1) Patients had needle biopsy and pathological diagnosis before chemotherapy. The clinical diagnosis was stage IIa-IIIc (T1-T4; N0-N3; M0). 2) The routine examination results of patients were normal before chemotherapy. 3) Patient underwent surgery after receiving NAC. *Exclusion criteria:* Patients have previously had local radiotherapy or systemic chemotherapy. After NAC, the pathology of the resected specimens was compared with the specimens before NAC. The compared results were classified into G1-G5 [7]. G1-G2 was defined as the non-significant group and G3-G5 was defined as the significant group.

There were 47 female patients aged from 24 to 55 years (mean 38.71 ± 11.23) with a total of 47 lesions in the significant group. There were 13 female patients aged from 26 to 63 years (mean 40.84±12.53) with a total of 13 lesions in the non-significant group. All patients and their families signed informed consent and the study was approved by the Ethics Committee of our hospital.

Research methods

Ultrasonography

Toshiba Aplio 400 color Doppler ultrasound imaging system with PTL-1005BT line array probe was applied in the present study. The system had elastic imaging technique and strain rate measurement software. Patients were examined before NAC and 1st, 2nd, 4th and 6th week after NAC. All patients were in supine position and their breasts were fully exposed. Each quadrant of the affected side of the breast was scanned. After finding lesion, a multi-section ultrasonic scan was performed to observe the location, shape, size, internal echo and measurement of the maximum diameter of the detected lesion. Then, lightly press and decompress were conducted at the speed of 2-3 per seconds in vertical direction under elastography mode. The sampling frame was set including lesion and surrounding tissue. After obtaining a stable elastic image, the lesion area (A) and the surrounding tissue area (B) at the same level were selected and the strain ratio (B/A) was calculated.

Pathological examination

Pathological examination was performed after surgical resection of the lesion. After 10% formalin fixation, dehydration, immersion, embedding in paraffin, serial sectioning and sealing, the collected tissues were pathologically studied. The lesions were diagnosed and recorded by two pathologists according to the kit instructions.

Statistics

Statistical analyses were performed by using SPSS19.0, Medcalc and graphpad. The numerical data were expressed as mean±SD and the t-test was used for comparison. The categorical variables were expressed as numbers and chi-square test was used for comparison. The maximum diameter and B/A values of the lesions before NAC and 1st, 2nd, 4th and 6th week after NAC were compared by repeated measurement of ANOVA. The ROC curve of the lesion diameter and B/A value were used to predict the value of NAC efficacy. P<0.05 was considered statistically significant.

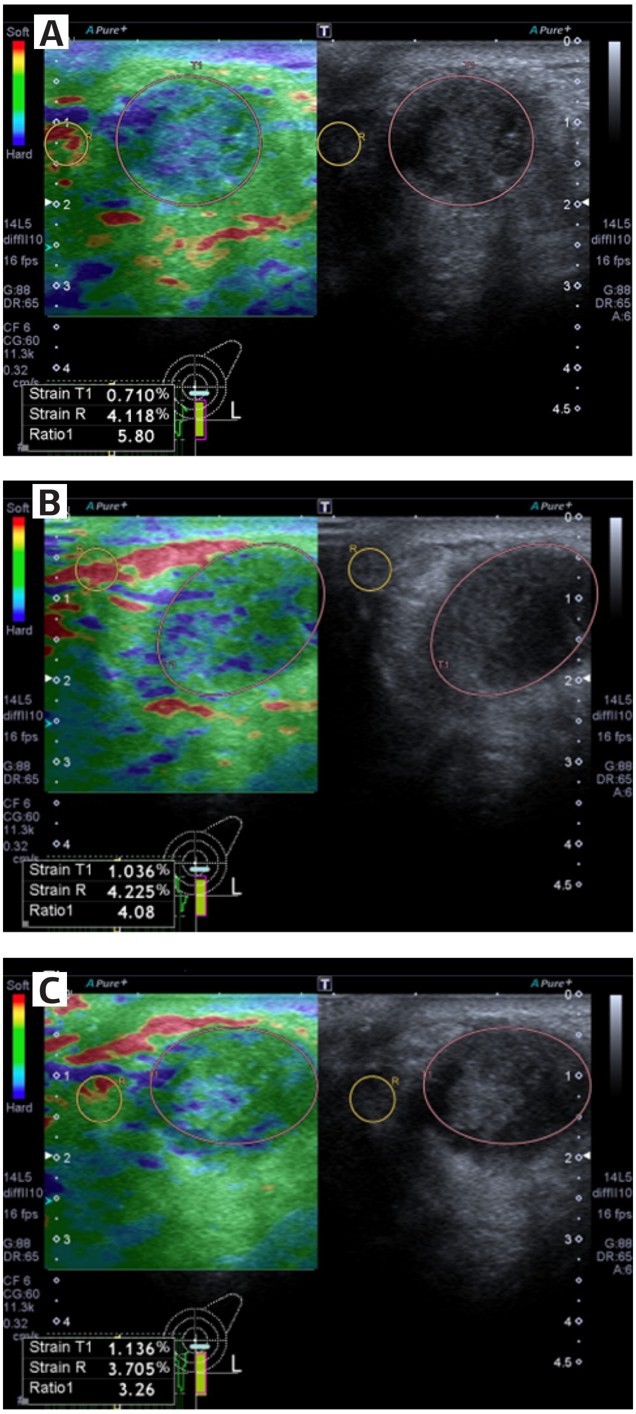

Figure 1. Changes of sonographic and elastic B/A values in breast lesions before and after NAC. **A:** Before NAC, the B/A value was 5.80; **B:** 4th week after NAC, the B/A value was 4.08; **C:** 6th week after NAC, the B/A value was 3.26.

Results

Ultrasound showed changes in lesions before and after NAC

There were 22 patients in G3, 6 patients in G4 and 9 patients in G5 with a total of 47 lesions in the significant group and 4 patients in G1, 9 patients in G2 with a total of 13 lesions in the non-significant group. Ultrasound sonograms and RTE images of lesions before and after NAC in breast cancer are shown in Figure 1A-C. In the RTE image, blue represented a harder tissue and red represented a softer tissue. The lesions were mainly blue before NAC. After NAC, the blue lesions were reduced in honeycomb shape and the green area gradually increased. The lesion reduction and elastic change in the significant group were more significant than those in the non-significant group.

Changes of maximum diameter and B/A value in breast lesions before and after NAC

The maximum diameter and B/A values of lesions in the two groups were recorded before and 1st, 2nd, 4th and 6th week after NAC. Repeated measurement of ANOVA found that the maximum diameter and B/A value showed a downward trend in the 6th week of NAC treatment. The two parameters in the significant response group were significantly lower than the non-significant response group before and after NAC. There was an interaction between the two parameters in the two groups before and after NAC. The above differences were statistically significant (all $p<0.05$). (Table 1 and Figure 2).

ROC curve analysis of early prediction of NAC efficacy with Δmaximal diameter and ΔB/A value

The AUC of Δmaximum diameter at 1st week of NAC (maximum diameter before NAC-maximum diameter 1st week after NAC) was 0.766, and the best diagnostic point was 0.59. The sensitivity was 53.85% and the specificity 91.49%.The AUC of ΔB/A value at 1st week of NAC (maximum B/A value before NAC-maximum B/A value 1st week after NAC) was 0.812, and the best diagnostic point was 3.09. The sensitivity was 69.23% and

Table 1. Changes of maximum diameter and B/A value in the significant and non-significant response groups before and after NAC

		Before NAC	*1st week*	*2nd week*	*4th week*	*6th week*	*Comparison within group*	*Comparison between group*	*Interaction Analysis*
Maximum diameter	Significant response group	4.52±1.56	4.01±1.42	3.68±1.35	2.03±1.09	1.49±0.63	8.092	3.726	9.036
	Non-significant response group	3.99±1.13	3.42±1.08	3.17±0.84	2.94±0.77	2.67±0.74	0.001	0.032	0.000
B/A value	Significant response group	17.15±7.87	12.28±5.29	8.38±4.28	6.43±3.18	4.24±3.17	8.632	3.516	5.963
	Non-significant response group	10.29±5.28	8.37±4.26	6.29±3.82	5.73±3.37	4.83±2.37	0.000	0.038	0.005

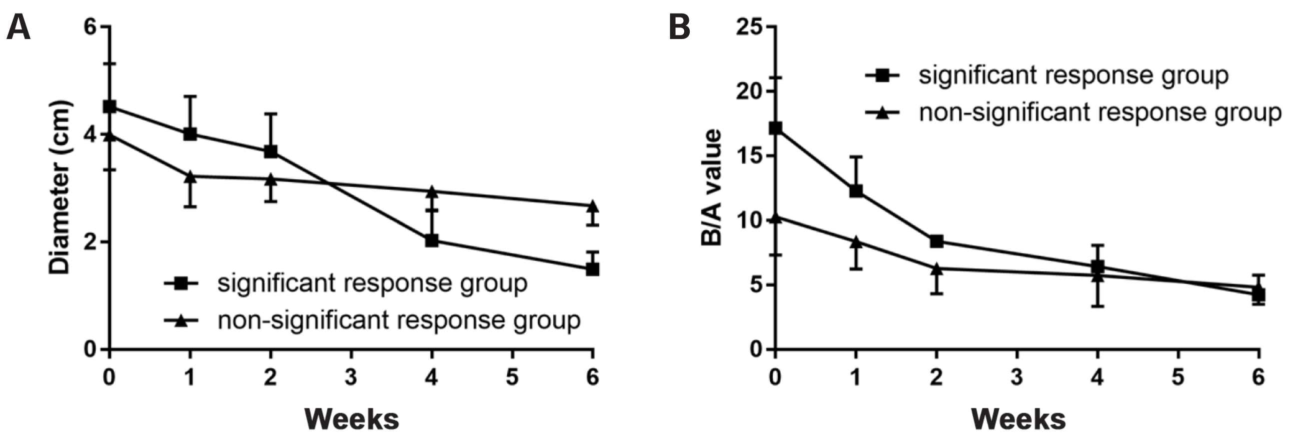

Figure 2. Trends of the maximum diameter and B/A value of lesions in the significant and non-significant response groups before and after NAC. **A:** Trend of the lesion's maximum diameter. $P_{within\ group}$= 0.001, $P_{between\ group}$= 0.032, $P_{interaction}$= 0.000; **B:** Trend of B/A values. $P_{within\ group}$= 0.000, $P_{between\ group}$= 0.038, $P_{interaction}$= 0.005.

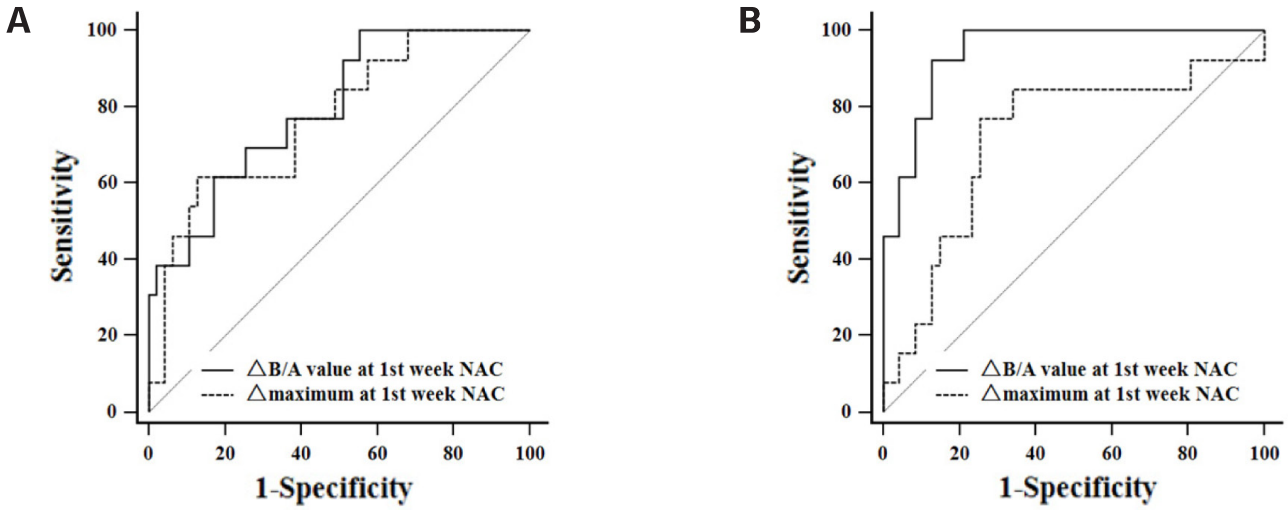

Figure 3. Lesions Δ maximum diameter and Δ B/A value early predicting the effect of NAC. **A:** lesions Δ maximum diameter and ΔB/A values at 1st week predicting the effect of NAC. The difference in AUC was not statistically significant (p=0.665); **B:** lesions Δ maximum diameter and ΔB/A values at 2nd week predicting the effect of NAC. The AUC of ΔB/A values was higher than Δ maximum diameter (p=0.003).

the specificity 80.85%. The difference in AUC between the two was similar and was not statistically significant (z=0.433, p=0.665; Figure 3A). The AUC of Δmaximum diameter at 2nd week of NAC was 0.610, and the best diagnostic point was 0.74 cm. The sensitivity was 61.54% and the specificity 74.47%. The AUC of ΔB/A value at 2nd week of NAC was maximal (0.944), and the best diagnostic point was 5.64. The sensitivity was 92.31% and the specificity 87.23%.The AUC of the ΔB/A value at 2nd week of NAC was the largest, which was significantly higher than the Δ maximum diameter, and the difference was statistically significant (z=3.026, p=0.003; Figure 3B).

Discussion

Predicting the efficacy of NAC in advance can help to screen patients with NAC resistance. It can avoid the toxic effects of chemotherapeutic drugs brought by multi-cycle treatment. Because of the honeycomb-like reduction in lesions after NAC, the lesion boundary of gray-scale ultrasound is difficult to define and it is also difficult in the measurement of maximum diameter in lesions [8-10]. Hence, the exploration for more accurate and effective evaluation of NAC efficacy indicators is of great significance. At present, elastography is used for tissue stiffness detection and is widely used in the diagnosis of benign and malignant tumors [11,12]. The B/A value of elastography is able to observe the change of hardness of lesions before and after NAC [13-15]. Hence, the present study explores the value of early prediction of NAC in breast cancer patient by comparing the data obtained by RTE and ultrasound.

In the present study, patients were divided into 5 grades according to Miler-Payne classification [16]. G1-G2 was the non-significant group and G3-G5 was the significant group. Ultrasound and elastography were observed at 1st, 2nd, 4th and 6th week of NAC. The results showed that the lesions gradually decreased during the course of treatment. Gray-scale ultrasound revealed that some lesions showed irregular honeycomb-like reduction. This suggested that conventional gray-scale ultrasound could not accurately evaluate the efficacy of NAC. The elastic imaging of the lesion changed from blue to green, suggesting that the lesion hardness was reduced and the tissue became soft. Repeated ANOVA evaluations found that the maximum diameter and B/A value of the two groups were significantly lower after NAC, suggesting that the above indicators are closely related to the state of the lesion. In contrast, the maximum diameter and B/A value of the significant group after NAC were smaller than that of the non-significant group, and the reduction of the significant group was greater. The interaction trends between the two groups implied that the two indicators can reflect changes in the lesion during the course of NAC.

The present study performed a ROC curve analysis of the Δmaximum diameter and the ΔB/A value at 1st and 2nd week of NAC. The purpose was to analyze the value of the Δmaximum diameter and ΔB/A value in predicting the efficacy of NAC. The results showed that the AUC of ΔB/A value at 2nd week of NAC was maximal (0.944), suggesting that it is the most valuable indicator for early prediction of NAC efficacy. Nevertheless, errors may occur because the lesions are in honeycomb-like reduction during the course of NAC and the sampling frame of elastography is still restricted by the operator's subjective operation. Hence, further multi-center research is needed to verify the results.

In summary, the present study found that the ΔB/A value of lesions in RTE can be used as an early predictor of NAC efficacy in breast cancer patients and it is helpful in developing breast cancer treatment plan.

Conflict of interests

The authors declare no conflict of interests.

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