Evaluation of tumor stiffness by elastography is predictive for pathological complete response to neoadjuvant chemotherapy in patients with breast cancer.

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Synopsis

This study investigated the value of elastography for prediction of response to chemotherapy in patients with breast cancer. We revealed that tumor stiffness measured by elastography was closely associated with the pathological response to neoadjuvant chemotherapy.

Abstract

Background: Breast elastography (EG), which can objectively evaluate tumor stiffness, has been useful for differentiation of benign and malignant breast lesions. However, the value of EG for prediction of response to systemic therapy is poorly understood.

Methods: The baseline evaluations of EG in 55 patients who received neoadjuvant chemotherapy were reviewed. We investigated the correlation between tumor stiffness and response to neoadjuvant chemotherapy. Tumor stiffness was evaluated using the Tsukuba elasticity scoring system.

Results: The mean EG scores were significant lower for the clinical and pathological complete response (pCR) groups than for the others. When we categorized patients into two groups according to tumor stiffness, 26 patients were assigned to the low EG group (soft, scores from I to III) and 29 patients were assigned to the high EG group (hard, score IV and V). The low EG group had significantly higher clinical CR and pCR rates than the high EG group (clinical CR, low EG group 38% vs. high EG group 10%, $P = 0.024$; pCR, low EG group 50% vs. high EG group 14%, $P = 0.003$, respectively). Furthermore, multivariate analysis indicated that ER, HER2, and low EG (odds ratio 13.04, 95% CI 1.19 to 458.28, $P = 0.035$) were independent predictive factors of pCR.

Conclusion: Our data demonstrate that tumor stiffness evaluated by EG bears predictive potential for response to neoadjuvant chemotherapy. Stiffness evaluated by EG may be recognized as a clinically significant tumor characteristic, comparable to other data obtained by functional imaging techniques.

INTRODUCTION

Breast elastography (EG) can objectively evaluate tumor or tissue stiffness in addition to morphology and vascularity, which can also be assessed by conventional ultrasonography [1]. So far, tumor stiffness has mainly been evaluated by palpation, and exploited to detect breast cancer. Similarly, the novel procedure EG has been helpful for diagnosing breast cancer, especially in differentiating benign from malignant lesions in clinical practice [2-4]. EG is a convenient non-invasive procedure and can provide the tumor stiffness as imaging information by means of measuring tissue strain induced by light compression in almost the same time as conventional ultrasound evaluation.

Basic research has revealed that tumor stiffness is associated with tumor progression including carcinogenesis [5, 6]. Tumor stiffness is a characteristic of the extracellular matrix and is modulated by collagen crosslinking. This mechanism involves several molecules such as integrin and lysyl oxidase, and promotes tumor progression through the enhancement of phosphatidylinositol-3 kinase (PI3K) signaling [5]. As is well known, activation of PI3K is a frequent event in malignant tumors, and promotes cell survival and treatment resistance.

Recently, neoadjuvant (preoperative) chemotherapy (NAC) has become the standard treatment, even in operable breast cancer [7]. Neoadjuvant and adjuvant chemotherapy are similar with respect to clinical survival [8], and NAC can increase the chances of successful breast conservation [9]. Moreover, a number of clinical trials examining the correlation between pathological complete response (pCR) to NAC and long-term survival have reported a strong association between these two outcomes [10]. Therefore, multidisciplinary approaches to predict the efficacy of NAC as surrogate marker for overall survival are in progress, including biology [11, 12], gene profiling [13, 14] and image examination [15, 16].

In fact, there are reports that magnetic resonance imaging (MRI) and positron emission

tomography (PET) findings are associated with responses to NAC for breast cancer [15-19]. Although these functional imaging methodologies have been assessed as predictors of treatment responses, less is known about the correlation between EG findings and sensitivity to breast cancer treatment. Therefore, if there is any correlation and we can elucidate it, EG would be useful as an adjunct to realize optimal individual treatment for breast cancer patient.

Accordingly, in our present study, we hypothesized that evaluation of tumor stiffness by EG has the potential to provide additional information useful in predicting the response to chemotherapy in clinical setting. To test this hypothesis, we investigated the baseline tumor stiffness in patients with operable breast cancer who received NAC and analyzed the correlations with clinical and pathological responses to NAC.

PATIENTS AND METHODS

Patients

We reviewed 117 consecutive patients with operable breast cancer, who received NAC at Kumamoto University Hospital from May 2007 to June 2011. Of these, 55 patients who underwent EG before NAC were enrolled in this study. All patients had histologically confirmed invasive breast cancer before NAC, and underwent surgery after completion of NAC. Our institutional review board approved this retrospective study, and informed consent was obtained from all patients.

EG protocol and analysis

Conventional ultrasonography and EG were obtained by using an EUB-8500 (Hitachi Medical Corporation, Tokyo, Japan) equipped with a 6 - 14 MHz linear transducer, performed by breast cancer oncologists with more than 2 years of experiences. First, we obtained B-mode images, and then performed elastographic evaluation of the mass-forming lesion. A region of interest (ROI) box was adjusted to include subcutaneous fat and pectoral muscle and was vertically compressed by the transducer under light pressure. (If the diameter of mass was large, we adjusted the position of transducer to include a sufficient area of surrounding normal gland in the ROI to correctly determine the difference in tumor stiffness compared with the surrounding area, with the mass lesion occupying less than 50% of ROI). Real time strain images illustrating the stiffness of the tissue were displayed with color tone according to the degree of strain: greatest strain (softest component), red; average strain, green; no strain (hardest component), blue. The tumor stiffness was evaluated using Tsukuba elasticity scoring system [1]: Score I, strain appears in the entire hypoechoic area; Score II, strain is not seen in

part of the hypoechoic areas; Score III, strain appears only in the peripheral areas; Score IV, no strain appears in the entire hypoechoic area; Score V, no distortion appears either in the hypoechoic area or surrounding areas.

Chemotherapy regimen

With regard to treatment regimen, briefly, 44 (80%) patients received sequential anthracycline- and taxane-containing chemotherapy, 6 (11%) patients received only anthracycline-containing chemotherapy, and 5 (9%) patients received only taxane-containing chemotherapy. Trastuzumab, which is a monoclonal antibody that interferes the human epidermal growth factor receptor type 2 (HER2), concurrently used with taxane was administered to all patients with HER2 positive breast cancer except one.

The details of anthracycline- and taxane-containing chemotherapy were as follows: 26 patients, 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by tri-weekly docetaxel (Doc); 13 patients, FEC followed by weekly paclitaxel (wPac); 5 patients, FEC; 4 patients, Doc and cyclophosphamide (TC); 2 patients, TC followed by FEC; 1 patient, wPac followed by FEC; 1 patient, FEC followed by TC; 1 patient, Doc followed by adriamycin and cyclophosphamide (AC), 1 patient, epirubicin and cyclophosphamide (EC); and 1 patient, wPac.

Evaluation of clinical and pathological responses

Clinical response was evaluated by comparing the longest diameter of the target lesions with the baseline measurement by ultrasonography or MRI evaluations based on the Response Evaluation Criteria in Solid Tumors (RECIST) [20]. Histological and biological examinations were performed at both diagnosis and surgery using the samples of core needle biopsy and

residual tumor in surgical specimens, respectively. Pathological response was assessed in surgical specimens of the breast with reference to the standards of the Japanese Breast Cancer Society [21]. In this study, a tumor with no residual invasive component of the breast was defined as pCR [10].

Assessment of tumor biology

Immunohistochemical staining was done according to manufacturer's recommended protocol. Briefly, estrogen receptor alpha (ER), progesterone receptor (PgR), HER2 expression, and Ki67 index were examined using the antibodies 6F11 (Ventana, Japan), 16 (Ventana), CB11 (Ventana), and MIB-1 (Dako, Glostrup, Denmark), respectively. ER and PgR status was considered positive when there was ≥1% of nuclear staining. HER2 positivity was indicated by 3+ immunohistochemical staining or fluorescence in situ hybridization with a threshold ratio of more than 2.0. Ki67 index was determined by counting at least 500 tumor cells in hot spots.

Statistical analysis

Statistical comparisons between elastographic evaluations and treatment responses were performed using the chi-square, Fisher's exact, and the student *t* tests. Univariate and multivariate analyses were performed with a logistic regression model. A two-sided *P* value <0.05 was considered to be statistically significant. The JMP 8.0 software package (SAS Institute Japan, Tokyo, Japan) was used for statistical analyses.

RESULTS

Patient characteristics and EG distribution

The patient characteristics at the baseline are shown in Table 1. Whole distributions of the baseline EG score were as follows: EG score was evaluated as II in 14 (25%) patients, III in 12 (22%) patients, IV in 19 (35%) patients, and V in 10 (18%) patients; there were no patients with an EG score of 1 in this study, in which almost all tumors were more than 2 cm in diameter (Table 1).

Clinical and pathological responses according to elastography score

Regarding the efficacy of NAC in all patients, clinical CR rate was 24% and pCR rate was 31% in the present study. In terms of clinical response to NAC with respect to each EG score, clinical CR rates were 43% for EG score II, 33% for score III, 11% for score IV, and 10% for score V, respectively ($P = 0.091$) (Fig. 1). In addition, the mean EG score was significantly lower for clinical CR group (mean score ± standard deviation, 2.8 ± 1.0) than for the others (3.6 ± 1.0) ($P = 0.017$). Similarly, in pathological response to NAC, pCR rates were 64% for EG score II, 33% for score III, 16% for score IV, and 10% for score V, respectively ($P = 0.010$) (Fig. 1) (Fig. 2). The mean EG score of pCR group was also lower compared with that of non-pCR group (2.8 ± 1.0 vs. 3.8 ± 1.0) ($P = 0.001$).

Correlation between elastographic value and treatment response

To more practically assess the correlation of response to NAC with tumor stiffness by EG, we categorized patients into two groups according to the stiffness with a cutoff value of EG score

III: 26 patients with low EG value (soft group, from score I to III) and 29 patients with high EG value (hard group, score IV and V) (Table 2). No significant differences were noted in clinical and pathological factors between the soft group and the hard group, except PgR status (P = 0.003). Based on this categorization, the soft group had significantly higher clinical CR and pCR rates than the hard group (clinical CR, soft group 38% vs. hard group 10%, P = 0.024; pCR, soft group 50% vs. hard group 14%, P = 0.003, respectively) (Table 3). Moreover, multivariate analysis indicated that the ER and HER2 were independent of low EG value as predictive factors of pCR (odds ratio 13.04, 95% CI 1.19 to 458.28, P = 0.035) (Table 4).

In addition, to rigorously exclude the possible influence of different regimens, we limited the analysis to the patients who received the sequential anthracycline and taxane chemotherapy (44/ 55 patients). Low EG values remained an independent predictive factor (odds ratio 12.3, 95% CI 1.08 to 426.0, P = 0.043) along with ER and HER2 status. We further limited the analysis to the patients without trastuzumab-containing chemotherapy (42/ 55 patients), because it has recently reported that the addition of trastuzumab to conventional chemotherapy significantly increased pCR rate [22]. As we expected, low EG values still predicted pCR in univariate analysis (odds ratio 8.85, 95% CI 1.25 to 179.3, P = 0.027).

DISCUSSION

This study revealed that tumor stiffness measured by EG was closely associated with the response to breast cancer chemotherapy. Relatively soft tumors were highly responsive to NAC and more frequently displayed pathological CR compared with hard tumors (pCR rate, 50% vs. 14%). Concerning the relevance of tumor stiffness to chemotherapeutic response, basic research reveals that increasing tissue stiffness induces tumor progression and modulates chemotherapeutic resistance [5, 6, 23]. Our findings that hard tumors were less responsive to chemotherapy than soft tumors might be reflect those basic mechanisms. Tumor stiffness, evaluated by EG, could be recognized in clinical practice as one of the tumoral and environmental characteristics that help clinicians to individualize breast cancer treatments, including NAC.

In the current analysis, we employed the NAC setting to elucidate the clinical implications of tumor stiffness. Because NAC to breast cancer is widely used in clinical practice around world, and response to chemotherapy, especially pCR, is considered as a major surrogate marker of subsequent prognosis [10]. Clarification of the correlation between tumor stiffness evaluated by EG and pCR rate could give us biological insight into the significance of tumor stiffness. Although numerous researchers in various fields are working on predictive factors for NAC [11-16], in clinical practice, ER and HER2 status remain conventional and predominant markers, consistent with our results. Briefly, ER-negative tumors respond better than ER-positive to NAC, and HER2-positive tumors are more responsive to conventional chemotherapy and highly responsive to trastuzumab-containing chemotherapy [22-24].

On the other hand, recent reports suggest that functional imaging techniques such as dynamic MRI, diffusion-weighted MRI and fluorodeoxy-D-glucose (FDG) PET can reveal tumor characteristics that may predict response to NAC. Park et al. and Iacconi et al. have reported that patients with a low pretreatment apparent diffusion coefficient (ADC) in

diffusion-weighted MRI analysis were more likely to respond to NAC [15, 19]. Moreover, Smith et al. reported that PET analysis showed high baseline FDG uptake in patients with pCR compared with patients who responded less [16]. Similarly, in the present study, we observed the correlation of EG evaluations with response to chemotherapy. Little has been reported previously regarding tumor stiffness and systemic therapy in clinical settings; however, like other functional imaging analyses, more such studies may be expected in the future.

Interestingly, in the analysis of clinical and pathological factors relevant to tumor stiffness, the relatively hard tumor group, which was less responsive to NAC, was more likely to be PgR-positive than the soft tumor group, although only among NAC-treated patients. Tumor stiffness is a characteristic of the extracellular matrix, and basic researchers have provided evidence that increasing extracellular matrix stiffness is involved in tumor progression in various tumors such as breast cancer [5], hepatocellular carcinoma [23], and glioma [25]. However, there are no reports about molecular correlation between tumor stiffness and PgR expression, thus further research is needed to determine whether PgR or ER expression is relevant to the effect of tumor stiffness on response to NAC.

At present, the main role of EG is to diagnose cancer and benign lesions in conjunction with conventional ultrasonography and to decrease unnecessary biopsies, based on tumor or tissue stiffness [2, 3]. The diagnosis depends on the principle that cancer is relatively hard compared with non-cancerous lesions; however, obviously, relatively soft cancers also exist. Until now EG has usually been performed on small tumors or lesions that need differential diagnosis, therefore, there has been little elastographic data about large tumors, which are easily diagnosed. Our current data, in which most of the tumors were more than 2 cm diameter, suggest that clinicians and technicians should evaluate tumor stiffness even if the tumor is large and clearly malignant, because we believe that evaluation of tumor stiffness by EG can predict treatment efficacy, as basic research has indicated. With accumulating evidence about

EG evaluations and the clinical and preclinical factors that influence the tumor stiffness [26, 27], clinicians may come to regard tumor stiffness as a not only a tool of differential diagnosis but as an indicator of treatment efficacy or prognosis.

However, our retrospective study has some limitations. A prospective analysis of a large number of patients with appropriate control of other factors is needed. In addition, we should be also impressed the procedural errors, although we tried to reduce them using by EG score grouping with a cutoff value of score III for analysis [2]. To improve reproducibility and the quality of the evidence, validation and standardization of EG procedure is also needed.

In conclusion, We suggest that tumor stiffness evaluated by EG is a meaningful tumor property related to treatment resistance. Based on this novel insight, more research is needed into correlations of EG stiffness with systemic therapy, such as hormonal therapy, which needs useful predictive factors [28]. Additional investigation should focus on whether changes in stiffness during systemic therapy can predict subsequent response or prognosis [29-32]. Elucidation of these issues might provide more information to help clinicians identify the patients suitable for various breast cancer treatments.

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FIGURE LEGENDS

FIG. 1. Correlations between elastographic score and treatment responses.

The relatively soft tumors showed good response to neoadjuvant chemotherapy. However, increasing stiffness induced chemotherapeutic resistance.

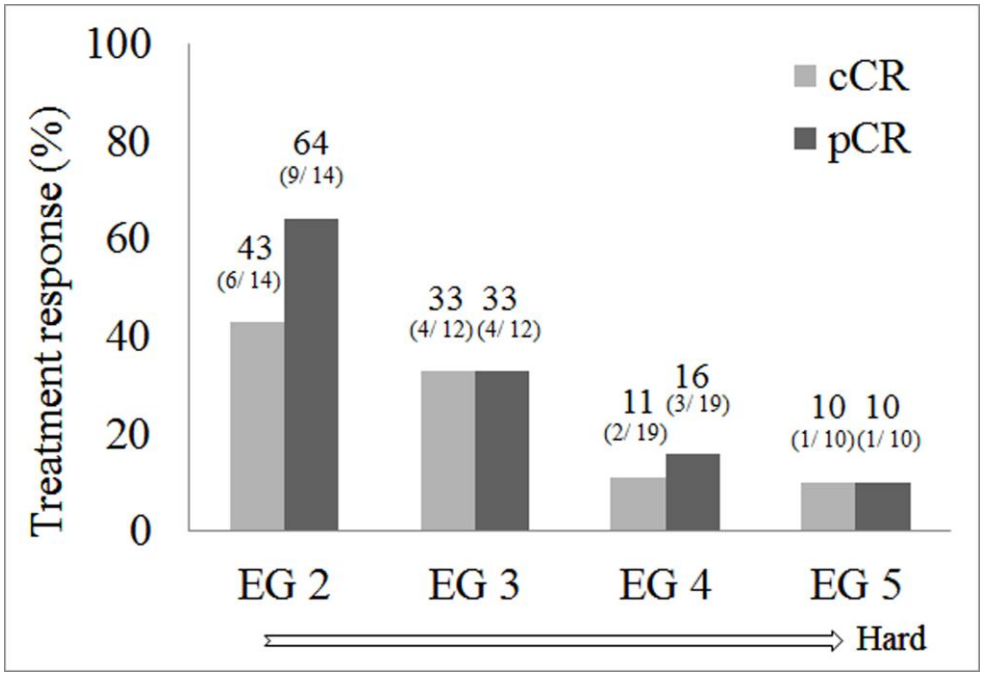

FIG. 2. Comparison of the tumors showed different elastographic values.

The tumor size and morphology were almost same for these tumors on evaluation of conventional ultrasonography.

Above: The tumor with elastographic score II resulted in pathological complete response due to neoadjuvant chemotherapy. This tumor was also calculated fat lesion strain ratio.

Below: The tumor with elastographic score IV did not resulted in pathological complete response after neoadjuvant chemotherapy.

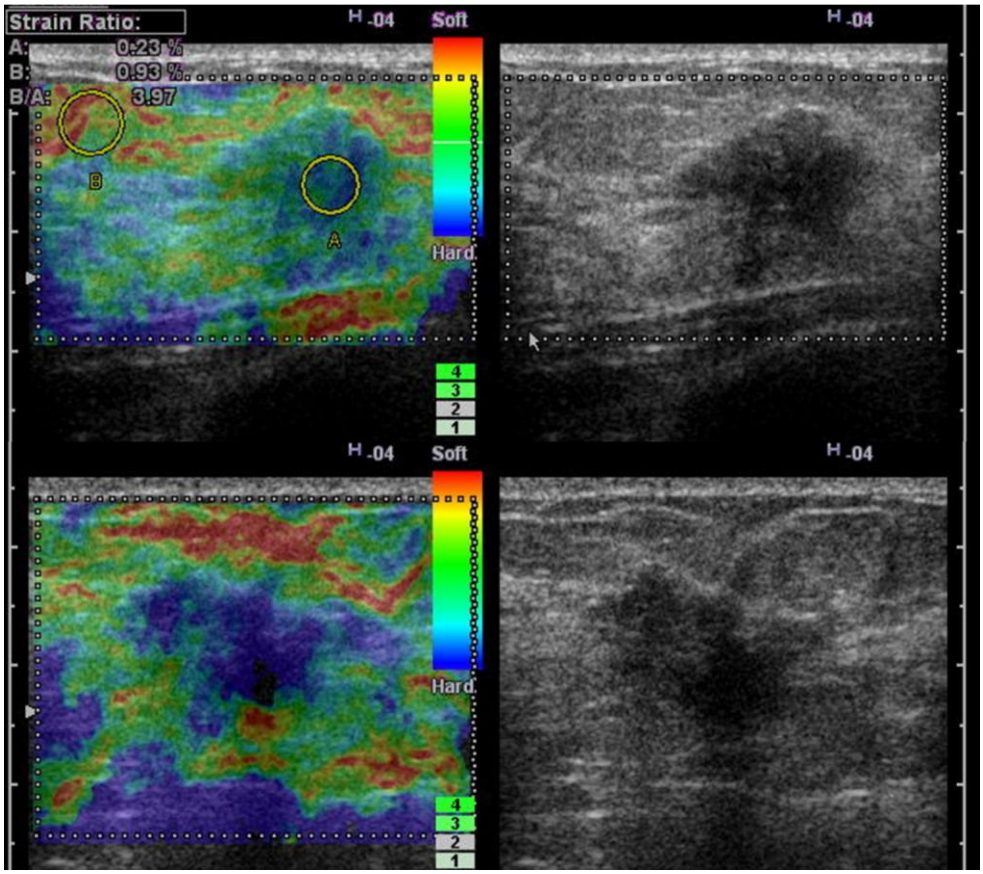
Strain Ratio:
A: 0.23 %
B: 0.93 %
B/A: 3.97
B
A
H -04
Soft
Hard
4
3
2
1
H -04
H -04
Soft
Hard
4
3
2
1
H -04

TABLE 1

Patient Characteristics at Pretreatment

Characteristic	No. of Patients (%) (n = 55)
Age (years)	
Median	52
Range	30 - 69
Menopausal status	
Premenopausal	22 (40)
Postmenopausal	33 (60)
Tumor size	
T1	9 (16)
T2	33 (60)
T3	8 (15)
T4	5 (9)
LN metastasis	
Positive	41 (75)
Negative	14 (25)
Estrogen receptor	
Positive	40 (73)
Negative	15 (27)
Progesterone receptor	
Positive	31 (56)
Negative	24 (44)
HER2	
Positive	14 (25)
Negative	41 (75)

Subtype	
ER (+) HER2 (-)	34 (62)
ER (+) HER2 (+)	5 (9)
ER (-) HER2 (+)	9 (16)
Triple negative [a]	7 (13)
Nuclear grade	
1	20 (36)
2	20 (36)
3	14 (26)
Unknown	1 (2)
Ki67 index	
Median, % (range)	30 (5 - 78)
Low [b]	11 (20)
High	41 (75)
Unknown	3 (5)
Histology	
IDC	53 (96)
Special type [c]	2 (4)

LN, lymph node; HER2, human epidermal growth factor receptor type 2; ER, estrogen receptor; IDC, invasive ductal carcinoma

[a] Estrogen receptor negative, progesterone receptor negative and HER2 negative, [b] Cut off value: <14%, [c] Special type: medullary carcinoma and apocrine carcinoma.

TABLE 2

Clinical and Pathological Factors according to Elastography Score

Factors	Soft group [a] (low EG, n = 26) No. of patients (%)	Hard group [b] (high EG, n = 29) No. of patients (%)	*P* value
Menopausal status			0.271
Premenopausal	8 (31)	14 (48)	
Postmenopausal	18 (69)	15 (52)	
Tumor size			0.584
<30 mm	16 (62)	20 (69)	
≥30 mm	10 (38)	9 (31)	
LN metastasis			1.000
Positive	19 (73)	22 (76)	
Negative	7 (27)	7 (24)	
Estrogen receptor			0.129
Positive	16 (62)	24 (83)	
Negative	10 (38)	5 (17)	
Progesterone receptor			0.003
Positive	9 (35)	22 (76)	
Negative	17 (65)	7 (24)	
HER2			0.215
Positive	9 (35)	5 (17)	
Negative	17 (65)	24 (83)	
Subtype			0.170
ER (+) HER2 (-)	13 (50)	21 (72)	
ER (+) HER2 (+)	2 (8)	3 (10)	
ER (-) HER2 (+)	7 (27)	2 (7)	
Triple negative [c]	4 (15)	3 (10)	
Nuclear grade			0.939
1	10 (38)	10 (36)	

2	9 (35)	11 (39)	
3	7 (27)	7 (25)	
Ki67 index [d]			0.499
Low	7 (27)	4 (15)	
High	19 (73)	22 (85)	
BMI			1.000
<25	21 (81)	23(79)	
≥25	5 (19)	6 (21)	
Breast density on MMG			0.586
Light [e]	14 (54)	12 (43)	
Dense [f]	12 (46)	16 (57)	

EG, elastography; LN, lymph node; ER, estrogen receptor; HER2, human epidermal growth factor receptor type 2; BMI, body mass index; MMG, mammography. .

[a] Elastography score 1 to 3, [b] Elastography score 4 and 5, [c] ER negative , progesterone receptor negative, and HER2 negative, [d] Cut off value: <14%, [e] Almost entirely fat and scattered fibroglandular densities, [f] heterogeneously dense and extremely dense based on BI-RADS.

TABLE 3

Clinical and Pathological Responses according to Elastography Score

Responses	Soft group [a] (low EG, n = 26) No. of Patients (%)	Hard group [b] (high EG, n = 29) No. of Patients (%)	*P* value
Clinical response			0.024
CR	10 (38)	3 (10)	
PR	12 (46)	23 (79)	
SD	4 (15)	3 (10)	
PD	0 (0)	0 (0)	
Pathological response			0.003
pCR	13 (50)	4 (14)	
non pCR	13 (50)	25 (86)	

EG, elastography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathological complete response

[a] Elastography score 1 to 3. [b] Elastography score 4 and 5.

TABLE 4

Univariate and Multivariate Analyses of Factors Influencing Pathological Complete Response

Characteristic		Univariate		Multivariate	
		Odds (95% CI)	*P* value	Odds (95% CI)	*P* value
ER	(positive vs. negative)	0.04 (0.01, 0.15)	<0.0001	0.06 (0.00, 0.78)	0.030
PgR	(positive vs. negative)	0.02 (0.00, 0.10)	<0.0001	0.32 (0.01, 7.41)	0.469
HER2	(positive vs. negative)	43.20 (8.80, 340.04)	<0.0001	51.85 (3.79, 2660.85)	0.001
EG value [a]	(low vs. high)	6.25 (1.81, 25.89)	0.003	13.04 (1.19, 458.28)	0.035
Menopausal	(post vs. pre)	4.67 (1.27, 22.68)	0.019	1.27 (0.08, 25.15)	0.864
Tumor size	(≥30 vs. <30 mm)	1.01 (0.98, 1.05)	0.487		
LN metastasis	(positive vs. negative)	0.32 (0.09, 1.15)	0.080		
Nuclear grade [b]	(high vs. low)	3.00 (0.84, 10.98)	0.090		

CI, confidence interval; ER, estrogen receptor; PgR, progesterone receptor; EG, elastography; LN. lymph node

[a] Elastography score 1 to 3. [b] High, grade 3; low, grade 1 and 2.