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Correlation of the Strain Elastography-Derived Elasticity Scores with Prognostic Histologic Features, Immunohistochemical Markers, and Molecular Subtypes of Invasive Ductal Carcinoma

유방 탄성 초음파에서 침윤성 유관암의 탄성 수치와 예후 예측 인자로서의 조직학적 소견, 면역화학적 요소, 유방암의 분자아형과의 상관성에 관한 연구

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Purpose To investigate the correlation of the strain elasticity of breast cancer with histologic features, immunohistochemical markers and molecular subtypes that are known to be factors related to prognosis.
Materials and Methods B-mode ultrasound and strain elastography were performed in 123 patients (mean age, 53.4; range, 28–82) with invasive ductal carcinoma (IDC) (mean size, 1.54 cm; range, 0.4–7.0 cm). Histologic grade, lymph node (LN) status, lymphovascular invasion, immu-

nohistochemical biomarkers [estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), CK5/6, epidermal growth factor receptor, and Ki-67] and molecular subtypes were determined from surgical pathology reports. The relationships between these factors and elasticity scores were evaluated.

Results LN involvement was associated with a higher elasticity score which was statistically significant (p = 0.042). The tumor size, lymphovascular invasion, histologic grades, immunohistochemical markers and molecular subtypes had no significant correlation with the elasticity score (p > 0.05 for all). However, the IDCs with larger size and a positive lymphovascular invasion tended to have higher elasticity scores. Furthermore, higher histologic grade cancers and the HER2 overexpression-type tended to have lower elasticity scores.

Conclusion The elasticity score of IDC had a significant correlation with LN involvement but no statistically significant correlation with the histologic features, immunohistochemical markers or molecular subtypes.

Index terms Breast Neoplasms; Ultrasound; Elastography; Immunohistochemistry; Prognosis

INTRODUCTION

Breast screening is routinely performed by mammography. Ultrasound is a complementary tool to mammography, especially in patients with mammographically dense breast tissue. However, there is a large overlap in the sonographic features between benign and malignant lesions. In recent years, ultrasound elastography has been widely used for differentiation between malignant and benign breast lesions (1-4). It is known that breast cancer tissue is harder than the adjacent normal parenchyma, so this technique could provide complementary information about the stiffness of breast lesions (5). Ultrasound elastography could be easily performed in addition to B-mode ultrasound. Many studies have shown that ultrasound elastography can be used to help differentiate malignant breast lesions from benign breast lesions while improving the specificity and accuracy of ultrasound (1, 5, 6). Strain elastography (SE) and shear-wave elastography (SWE) are the two most frequently used ultrasound elastography techniques in the breast. In SE, stress is applied by repeated manual compression of the transducer, which provides a measurement of the deformed lesion relative to the surrounding normal tissue with a color display (1). The other technique, SWE, uses an acoustic radiation force impulse created by an ultrasound beam, which allows for the measurement of the propagation speed of shear waves within the tissue and quantifies the stiffness in either kilopascals or meters per second (7-10). Although they are different in terms of the forces measured and the imaging methods, they show an overall similar diagnostic performance in the differentiation between malignant and benign breast lesions (11).

Breast cancer is a heterogeneous disease with various morphologies, clinical courses, treatment responses and prognoses. Tumor size, lymph node status, histological type, histological grade, and lymphovascular invasion are the important prognostic histologic features (12-15). Traditional classification of invasive breast cancer is based on the clinicopathologic analysis of tumors, which includes invasive ductal, invasive lobular, mucinous (colloid), tubular, medullary and papillary carcinomas. This classification offers limited prognostic value and treat-

ment options. Recently, molecular characterization of breast cancer has allowed for a new classification that could offer prognostic value. The new subtypes of breast cancers were classified via an immunohistochemical expression of the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), CK5/6, epidermal growth factor receptor (EGFR) and Ki-67. These subtypes based on molecular classifications also showed different responses to treatment and contributed to personalized therapeutic options with receptor-targeted therapies (16-20).

Hormone receptor (HR)-negative cancers tend to be of a high grade, have a worse prognosis and lack a response to hormone therapy compared to HR-positive cancers (21). Although HER2 overexpression is associated with a high recurrent rate and mortality, a target agent was developed that has resulted in a reduction of the risk of recurrence and mortality in patients with HER2 overexpression (22). Also, it was known that basal markers, such as CK5/6 and/or EGFR, were associated with high-grade cancer and BRCA1 mutation and with a poor prognosis (23).

If there is a significant association between the elasticity information for a breast mass using SE and the histologic features, immunohistochemical markers, and molecular subtypes that are known as factors related to prognosis, we can use it to predict the prognosis of breast cancer in a non-invasive way.

Therefore, the objective of this study was to investigate the association between the elasticity scores of breast cancers and histopathologic variables known as prognostic factors.

MATERIALS AND METHODS

STUDY POPULATION

The Institutional Review Board approved and required neither patient approval nor patient informed consent for the review of their images and records (IRB No. XC17REDI0052).

From September 2009 to December 2012, we retrospectively studied 123 women (mean age, 53.4; range, 28–82) with 123 breast lesions that were confirmed by core needle biopsy to have invasive ductal carcinoma (IDC) (mean size, 1.54 cm; range, 0.4–7.0 cm) and underwent surgical treatment.

IMAGE DATA ACQUISITION

The breast lesions were evaluated via B-mode ultrasound and simultaneous real-time SE using a 14–6 MHz linear array transducer (EUB-8500; Hitachi Medical, Tokyo, Japan) by one of three board-certified radiologists, who were specialized in breast imaging for 10, 9, and 7 years, respectively. The radiologists obtained at least two orthogonal gray-scale images per lesion for the breast morphology and size. After that, they obtained strain elasticity images for the elasticity score for a lesion. The region of interest was set to include the entire focal lesion and surrounding normal tissue. Manual compression was applied to the ultrasound probe, and a semitransparent color map of the tissue stiffness was overlaid on the B-mode image. After examination, the radiologists who performed the B-mode ultrasound and SE recorded the information about the lesion and elasticity score using a 5-point scale without any histologic information. The scales of the SE are as follows: score 1, even strain throughout the en-

tire target lesion; score 2, even strain in most of the target lesion with some strain-free area showing a mosaic pattern of green and blue; score 3, strain only in the periphery of the lesion, not in the center; score 4, no strain in the entire lesion; and strain 5, no strain within the lesion and surrounding area of the target lesion (1).

HISTOPATHOLOGIC DATA ACQUISITION

All patients underwent surgical treatment (mastectomy, n = 90; conserving surgery, n = 33). For the immunohistochemical studies, formalin-fixed, paraffin-embedded tissue sections were stained with antibodies for ER (Novocastra, Newcastle upon Tyne, UK), PR (Novocastra), HER2 [EGFR-2 (ErbB-2); Ventana Medical Systems, Tucson, AZ, USA], HER1 (EGFR; Ventana Medical Systems), cytokeratin 5/6 (CK5/6; Dako, Glostrup, Denmark), and Ki-67 (MIB-1; Dako). ER and PR were determined by nuclear staining, which was graded from 0 to 8 using the Allred score. The results were categorized as positive when the total score, expressed as the sum of the proportion score and immunointensity score, was 3 or more. For HER2 evaluation, membranous staining was graded as follows: score 0, 1 +, 2 +, and 3 +. The HER2 status was deemed to be positive with a score of 3+ and negative with a score of 0 or 1 +. Tumors with a score of 2 + were sent for fluorescence *in situ* hybridization testing, performed using the PathVysion HER2 DNA Probe Kit (Abbott-Vysis, Des Plaines, IL, USA). This test determines the HER2 amplification in the event that the ratio of the HER2 gene signal to chromosome 17 signal is 2 or more, which is classified as positive. CK5/6 was scored as positive if any tumor cells were stained as cytoplasmic and/or membranous pattern, while EGFR was scored as positive when any tumor cells showed membranous immunoreactivities. Ki-67 was quantified as the percentage of cells that displayed nuclear staining among a total of at least 1000 tumor cells at high-power field. The molecular subtypes of breast cancer were stratified by ER, PR, and HER-2 status and were categorized as follows: luminal type (ER- and/or PR-positive, HER2-negative), HER2 overexpression type (ER- and PR-negative, HER2-positive), and triple-negative (ER-, PR-, and HER2-negative).

STATISTICAL ANALYSIS

The statistical analysis was performed twice; first, to compare the five-point elasticity scores with histologic feature, immunohistochemical status and molecular subtypes; and second, to compare the three-subgroup of elasticity scores (i.e., low elasticity, score 1–2; intermediate elasticity, score 3; high elastiscity, score 4–5), with above variables. For data analysis, either Chi-squared tests or Fisher's exact tests were used. The data were analyzed using statistical software (SAS, version 9.4; SAS Institute, Cary, NC, USA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The elasticity scores according to the pathologic features are shown in Table 1. Lymph node (LN) involvement was associated with higher elasticity scores (positive group, mean elasticity score = 3.44; negative group, mean elasticity score = 2.86) (Fig. 1). Although the difference was not statistically significant in the five-point elasticity score analysis (p = 0.093), it

Table 1. Correlation of Pathologic Features and Presence of Hormone Receptors with the Elasticity Scores

	Elasticity Score						p-Value	
	Score 1 (n = 10)	Score 2 (n = 26)	Score 3 (n = 55)	Score 4 (n = 19)	Score 5 (n = 13)	Mean	5-Score	3-Subgroups*
Size, cm							0.226	0.664
< 1 (n = 37)	7 (18.9)	6 (16.2)	15 (40.5)	5 (13.5)	4 (10.8)	2.81		
1–2 (n = 53)	3 (5.7)	11 (20.0)	27 (50.9)	7 (13.2)	5 (9.4)	3.0		
≥ 2 (n = 33)	0 (0)	9 (27.3)	13 (39.4)	7 (21.2)	4 (12.1)	3.18		
Histologic grade							0.812	0.590
Grade 1 (n = 29)	3 (10.3)	5 (17.2)	12 (41.4)	5 (17.2)	4 (13.8)	3.07		
Grade 2 (n = 69)	6 (8.7)	13 (18.8)	31 (44.9)	11 (15.9)	8 (11.6)	3.03		
Grade 3 (n = 23)	1 (4.3)	8 (34.8)	11 (47.8)	2 (8.7)	1 (4.3)	2.74		
Lymph node							0.093	0.042
Positive (n = 27)	0 (0.0)	5 (18.5)	10 (37.0)	7 (25.9)	5 (18.5)	3.44		
Negative (n = 96)	10 (10.4)	21 (21.9)	45 (46.9)	12 (12.5)	8 (8.3)	2.86		
Lymphovascular invasion							0.387	0.816
Positive (n = 31)	3 (9.7)	5 (16.1)	14 (45.2)	3 (9.7)	6 (19.4)	3.13		
Negative (n = 91)	7 (7.7)	21 (23.1)	41 (45.1)	15 (16.5)	7 (7.7)	2.93		
Estrogen receptor							0.646	0.301
Positive (n = 97)	7 (7.2)	19 (19.6)	43 (44.3)	17 (17.5)	11 (11.3)	3.06		
Negative (n = 26)	3 (11.5)	7 (26.9)	12 (46.2)	2 (7.7)	2 (7.7)	2.73		
Progesterone receptor							0.733	0.820
Positive (n = 86)	8 (9.3)	18 (20.9)	39 (45.3)	14 (16.3)	7 (8.1)	2.93		
Negative (n = 37)	2 (5.4)	8 (21.6)	16 (43.2)	5 (13.5)	6 (16.2)	3.14		
HER-2							0.436	0.704
Positive (n = 33)	1 (3.0)	9 (27.3)	16 (48.5)	3 (9.1)	4 (12.1)	3.0		
Negative (n = 88)	9 (10.2)	17 (19.3)	37 (42.0)	16 (18.2)	9 (10.2)	2.99		
CK5/6							0.473	0.698
Positive (n = 16)	2 (12.5)	4 (25.0)	6 (37.5)	1 (6.3)	3 (18.8)	2.94		
Negative (n = 105)	8 (7.6)	22 (21.0)	49 (46.7)	17 (16.2)	9 (8.6)	2.97		
EGFR							0.191	0.889
Positive (n = 18)	4 (22.2)	2 (11.1)	8 (44.4)	2 (11.1)	2 (11.1)	2.78		
Negative (n = 96)	5 (5.2)	22 (22.9)	44 (45.8)	15 (15.6)	10 (10.4)	3.03		
Ki-67							0.458	0.306
Positive (n = 56)	4 (7.1)	16 (28.6)	24 (42.9)	7 (12.5)	5 (8.9)	2.88		
Negative (n = 67)	6 (9.0)	10 (14.9)	31 (46.3)	12 (17.9)	8 (11.9)	3.09		

Data are numbers of cases, and data in parentheses are percentages.
*p-value obtained by dividing the five elasticity scores into three groups [i.e., low (score 1 and 2), intermediate (score 3), and high elasticity (score 4 and 5)] and comparing the three groups with respect to the variables.
CK5/6 = cytokeratin 5/6, EGFR = epidermal growth factor receptor, HER2 = human epidermal growth factor receptor 2

was statistically significant ($p = 0.042$) according to the three-subgroup analysis. The larger-sized cancers tended to have higher elasticity scores (more than 2 cm, mean elasticity score 3.18; between 1 cm and 2 cm, mean elasticity score 3; less than 1 cm, mean elasticity score 2.81), although there was no statistical significance with either statistical analysis, i.e., the five-point elasticity score analysis or the three-subgroup analysis of elasticity score. The histo-

Fig. 1. A 57-year-old woman diagnosed with an invasive ductal carcinoma (1 cm in size, T1/N1, histologic grade 2) in the left breast.
A. B-mode ultrasound shows a hypoechoic mass with an irregular shape and a spiculated margin.
B. Ultrasound elastography shows a mass with a higher elasticity score (score 4).
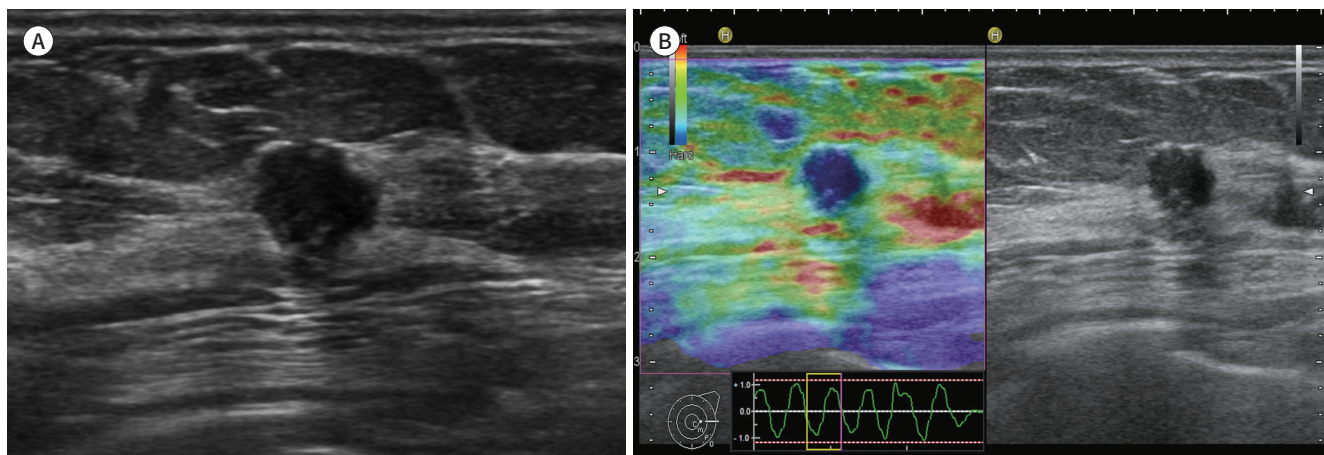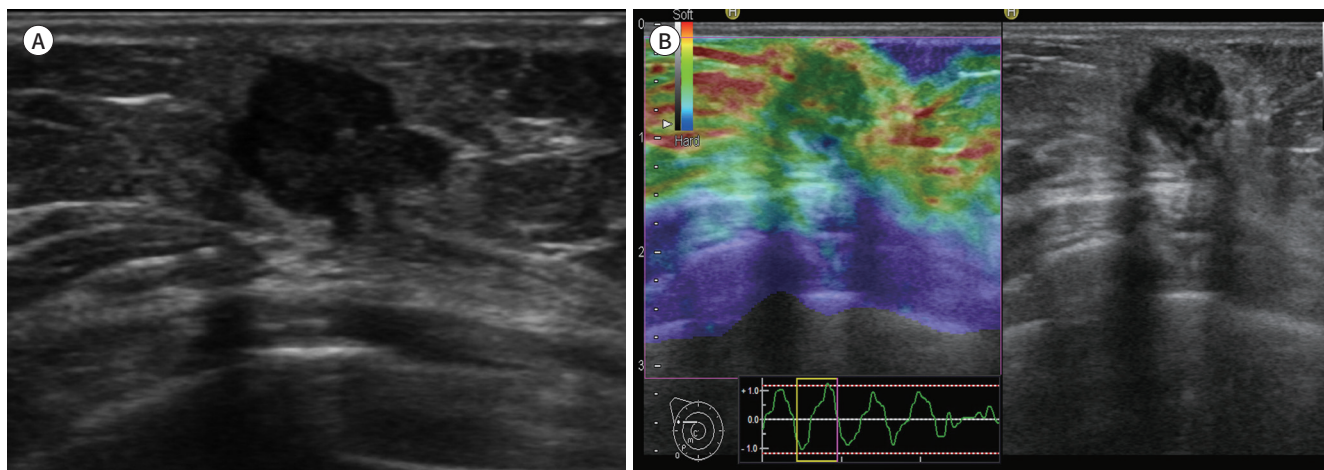

Fig. 2. A 56-year-old woman diagnosed with an invasive ductal carcinoma (1.5 cm in size, T1/N0, histologic grade 3) in the right breast.
A. B-mode ultrasound shows a hypoechoic mass with an irregular shape, an angular margin, and posterior shadowing.
B. Ultrasound elastography shows a mass with a lower elasticity score (score 1).

logic grades 1 and 2 cancers (mean elasticity scores 3.07 and 3.03, respectively) had similar average elasticity scores as well, and grade 3 cancers had a lower average elasticity score (mean elasticity score 2.74) (Fig. 2) than the grades 1 and 2 cancers (mean elasticity scores 3.07 and 3.03, respectively), but this was not significant ($p = 0.812$ and $p = 0.590$, respectively). The cancers with lymphovascular invasion tended to have higher elasticity scores (positive group, mean elasticity score 3.13; negative group, mean elasticity score 2.93), but this was not statistically significant ($p = 0.387$ and $p = 0.816$, respectively).

The elasticity scores according to the HR status are also shown in Table 1. ER-positive cancers are associated with higher mean elasticity scores, and PR-, EGFR-, and Ki-67-positive cancers were associated with lower mean elasticity scores. However, the differences were not statistically significant.

The elasticity scores according to tumor molecular subtypes are shown in Table 2. HER2 overexpression-type cancers had lower scores (mean elasticity score 2.6) than the other types

Table 2. Correlation of Breast Cancer Subtypes with the Elasticity Scores

	Elasticity Score						p-Value	
	Score 1	Score 2	Score 3	Score 4	Score 5	Mean	5-Score	3-Subgroup*
Luminal (n = 101)	8 (7.9)	19 (18.8)	46 (45.5)	17 (16.8)	11 (10.9)	3.04	0.351	0.156
HER2 overexpression (n = 10)	0 (0)	4 (40.0)	6 (60.0)	0 (0.0)	0 (0.0)	2.60		
Triple negative (n = 12)	2 (16.7)	3 (25.0)	3 (25.0)	2 (16.7)	2 (16.7)	2.92		

Data are numbers of cases, and data in parentheses are percentages.
*p-value obtained by dividing the five elasticity scores into three groups [i.e., low (score 1 and 2), intermediate (score 3), and high elasticity (score 4 and 5)] and comparing the three groups with respect to the variables.
HER2 = human epidermal growth factor receptor 2

Fig. 3. A 41-year-old woman diagnosed with an invasive ductal carcinoma (2.8 cm in size, T2/N3, histologic grade 3) in the right breast.
A. B-mode ultrasound shows a hypoechoic lesion with an irregular shape and angular margin.
B. Ultrasound elastography shows a mass with a lower elasticity score (score 2).
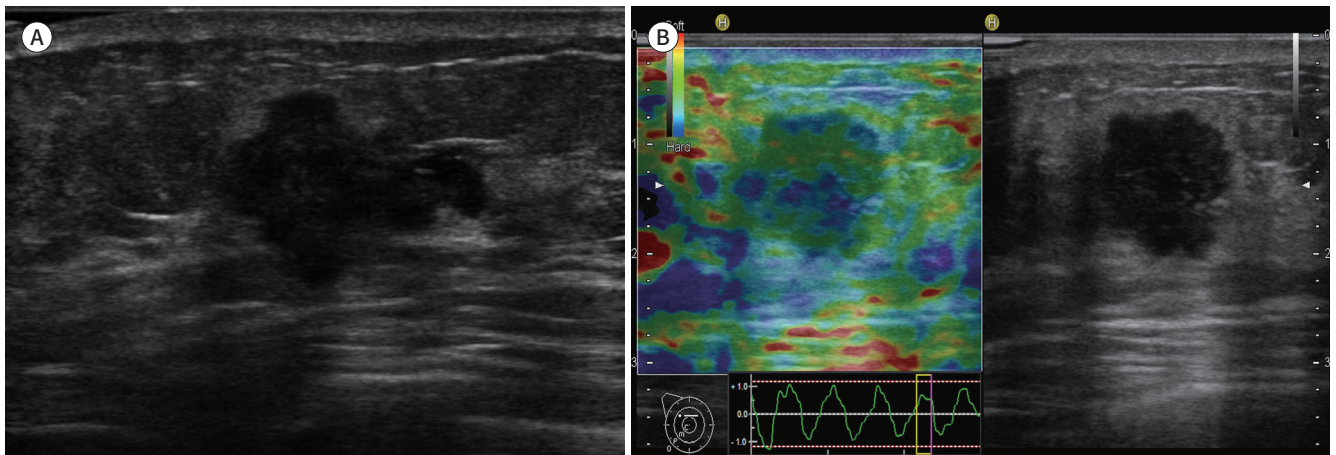
(luminal type, mean elasticity score 3.04; triple-negative type, mean elasticity score 2.92) (Fig. 3), but this was not statistically significant (p = 0.351 and p = 0.156, respectively).

DISCUSSION

In this study, high elasticity scores were only associated with a positive LN status in the three-subgroup of elasticity score analysis, which was divided into a low (score 1–2), intermediate (score 3) and high elasticity score (score 4–5).

A few studies have reported various results regarding the correlation between strain elasticity of breast cancer and prognostic factors. Kim et al. (24) reported that tumors with axillary LN metastasis had a higher elasticity ratio than tumors without axillary LN metastasis. They also observed that tumors with lymphovascular invasion were associated with a higher strain ratio than tumors without lymphovascular invasion. They did not find any correlation of the elasticity strain ratio of breast cancers with tumor size, the ER, PR, HER2, p53, or Ki-67 status. We had similar results.

Although Soyder et al. (25) demonstrated that higher histologic grade tumors showed higher elasticity scores and Ki-67-positive tumors showed lower elasticity scores (among elasticity scores of 4 and 5), in our study, high histologic grade cancers showed low elasticity scores

and Ki-67-positive tumors showed lower elasticity scores.

Based on SWE, Evans et al. (26), observed that poor prognostic factors for breast cancers, such as higher histologic grade, larger tumor size, lymph node involvement, tumor type, and vascular invasion, were associated with higher mean stiffness values. Choi et al. (27) also demonstrated that tumors with negative ER, negative PR, positive p53, positive Ki-67 status, higher nuclear grade, and histologic grade had higher SWE ratios. Chang et al. (28) demonstrated that a large tumor size, higher histologic grade, positive LN status, negative ER status, and negative PR status had a high mean stiffness via SWE. Youk et al. (29) demonstrated that a higher histologic grade and lymphovascular invasion were associated with a higher mean elasticity value by SWE. Au et al. (30) reported significant correlations between larger cancer size, LN involvement, lymphovascular invasion, positive HER2 and higher SWE parameters. In summary, these studies by SWE showed that poor prognostic factors, such as larger tumor size, higher histologic grade, positive LN status, lymphovascular invasion, negative ER status and positive HER2 status, were associated with higher SWE ratios (26-30).

Basic research has revealed that increasing tumor stiffness is associated with tumor progression (30). Tumor stiffness is a characteristic of the extracellular matrix. Collagen cross-linking is a contributor to tumor matrix stiffening, which leads to an enhancement of integrin signaling and tumor invasiveness (31). Also, a larger tumor elicits more desmoplastic reaction, increased cellularity, angiogenesis, and edema in the tumor and in the periphery compared to smaller tumors. These are all contributors to tumor stiffness. Other poor immunohistologic prognostic factors are associated with larger tumor size, resulting in higher elasticity values (32).

However, there are discrepant results among studies regarding histologic grade. Chang et al. (28) suggested that higher histologic grade cancers were associated with higher mean stiffness. They explained that the complicated combination of cellularity, microvessel density, necrosis, and fibrosis may induce greater stiffness in higher histologic grade cancers compared to lower histologic grade cancers. However, Au et al. (30) suggested that a desmoplastic reaction was more marked in grade 1 cancers compared to grade 3 cancers, so grade 1 cancers were expected to be harder than grade 3 cancers. This is consistent with our results, which show that lower histologic grade cancers had higher elasticity scores.

This study has several limitations. First, this was a retrospective study with a relatively small sample size. Further investigation in a larger study population is necessary. Second, we did not assess any inter- or intra-observer variance among the three radiologists who performed the SE. However, these radiologists were experts in breast imaging, each with more than 10 years of experience in breast imaging and more than 2 years of experience in performing SE. Finally, this study only involved two institutions using the same strain-elastography ultrasound device from a single manufacturer.

In conclusion, we observed that IDC with a positive LN status had a higher elasticity score with an observed statistical significance. We also observed that IDC with a larger size, lower histologic grade, and positive lymphovascular invasion tended to have higher elasticity scores and that HER2 overexpression-type cancers had lower elasticity scores than other subtypes, although there were no statistical differences. Further prospective studies with larger populations might be required.

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대한영상의학회지

유방 탄성 초음파에서 침윤성 유관암의 탄성 수치와 예후 예측 인자로서의 조직학적 소견, 면역화학적 요소, 유방암의 분자아형과의 상관성에 관한 연구

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목적 탄성 초음파에서 유방암의 탄성 지수와 유방암의 예후 예측인자로 알려진 조직학적 특성, 면역화학적 인자, 분자 아형과의 관계를 비교하여, 탄성 지수가 유방암의 예후를 예측할 수 있는지 알아보고자 한다.

대상과 방법 123명(평균 연령, 53.4세; 연령 범위 28~82세)의 침습성 유관암(평균 크기, 1.54 cm; 크기 범위, 0.4~7.0 cm) 환자를 대상으로 B-모드 초음파와 탄성 초음파를 시행하였다. 각 유방암의 조직학적 등급, 림프절 전이, 림프관 혈관강 침습, 면역화학적 생체표지자(에스트로겐 수용체, 프로게스테론 수용체, 인간 표피성장인자수용체 2, CK5/6, 표피성장인자 수용체, Ki-67) 그리고 분자아형(luminal형, HER2 과발현형, 삼중음성형) 등을 수술 후 병리보고서를 통해 분류하였다. 이 결과와 유방암의 탄성 지수의 관계를 평가하였다.

결과 림프절 전이가 있는 경우 통계적으로 유의미한 높은 탄성 지수를 보였다. 통계적으로 유의미하지는 않았지만, 종양이 크고, 림프관 혈관강 침습이 있을수록 탄성 지수는 증가하고, 조직학적 등급이 낮을수록 탄성 지수는 낮았다. 유방암의 분자 아형 중에는 HER2 과발현형이 다른 아형보다 낮은 탄성 지수를 보였다.

결론 침윤성 유관암의 림프절 전이가 있는 경우 통계적으로 유의한 높은 탄성 지수를 보이고, 다른 예후 예측 인자인 조직학적 특성, 면역화학적 인자, 분자 아형은 탄성 지수와 통계적으로 유의한 연관성이 없었다.

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