의학 석사 학위논문

관내상피암의 유방보존술 후 국소재발암 발생 예측을 위한 종양주변실질의 역동자기공명영상 조영증가율 평가

Background Parenchymal Signal Enhancement Ratio on Preoperative MRI May Predict Local Recurrence in Ductal Carcinoma in Situ Patients after Breast conserving Surgery

2013년 2월

서울대학교 대학원

의학과 영상의학 전공

김 선 아

ABSTRACT

Background Parenchymal Signal Enhancement Ratio on Preoperative MRI May Predict Local Recurrence in Ductal Carcinoma In Situ Patients after Breast Conserving Surgery

Sun Ah Kim

Department of Radiology

The Graduate school

Seoul National University

Purpose: To retrospectively investigate whether the signal enhancement ratio (SER) of the background parenchyma around the tumor on dynamic contrast enhanced MR imaging was associated with ipsilateral breast tumor recurrence (IBTR) in breast ductal carcinoma in situ (DCIS) patients after breast conserving surgery (BCS).

Materials and Methods: Between 2004 and 2009, 215 consecutive women (median age, 47years; range, 24−74years) with pure DCIS (mean size, 2.90cm ± 1.99 ; range, 0.2cm − 9.8cm) who underwent preoperative MRI, curative BCS and had at least 2−year follow−up data were identified. Their clinicopathologic features (age, menopausal status, surgery type, adjuvant therapy, ER, PR, HER2 status, nuclear grade, margin width) and MRI features [lesion size, morphology, fibroglandular density, background parenchymal enhancement grade, parenchymal SER defined as $(S_e-S_p)/(S_d-S_p)$, where S_p, S_e, and S_d represent the signal intensity on the precontrast, early postcontrast, and delayed postcontrast images] were analyzed. Receiver operating characteristic curves were used to determine the best cut−off value of variables for the prediction of IBTR. The reproducibility of the SER measurements was evaluated by using the intraclass correlation coefficient (ICC). RFS was estimated using the Kaplan−Meier method. A multivariate Cox proportional hazards model was used to determine associations between survival outcome and MRI variables, adjusting for clinicopathologic variables.

Results: There were 15 (7.0%, 15 of 215) ipsilateral breast tumor recurrences (9 DCIS, 6 invasive recurrences). The median follow−

up period for the no recurrence group (n=200) was 48 months (range 27−100 months). The ICC between the two radiologists was 0.852 (95% confidence interval [CI]: 0.811, 0.885; P < .001) for measurements of the SER, which indicates excellent agreement. On multivariate analysis, high mean background parenchymal SER around tumor was an independent factor associated with early IBTR : The hazard ratio (HR) for high SER were 17.837 (95% CI: 4.958, 64.472 ; *P*< .001), and 10.136 (95% CI: 3.392, 30.288; *P*< .001) for reader 1 and reader 2, respectively. Omission of the adjuvant endocrine therapy and larger size of tumor measured at surgical specimen were also found to be independent poor prognostic factors for IBTR on multivariate analysis.

Conclusion: High SER in the background parenchyma around the tumor, omission of adjuvant endocrine therapy and larger tumor size at specimens were independent factor associated with IBTR in breast DCIS patients treated with BCS.

Keywords: Breast, MRI, signal enhancement ratio, ductal carcinoma in situ, recurrence, survival, background parenchyma

Student number: 2011−21826

List of tables

List of figures

List of abbreviations and symbols

SER : signal enhancement ratio

DCE-MR : dynamic contrast enhanced MR

DCIS : ductal carcinoma in situ

IBTR : ipsilateral breast tumor recurrence

BCS : breast conserving surgery

ROI : region of interest

ICC : intraclass correlation coefficient

RFS : recurrence free survival

HR : hazard ratio

CI : confidence interval

RT : radiation therapy

TPN : triple negative

BPE : background parenchymal enhancement

FGT : fibroglandular tissue

ROC : receiver operating characteristic

Contents

INTRODUCTION

The diagnosis of ductal carcinoma in situ (DCIS) has increased markedly since the early 1980s with the introduction of screening mammography (1, 2). In 2011, 57,650 new diagnoses of in situ breast cancer were identified in US, and DCIS was the fourth most commonly diagnosed malignancy in women (3, 4). Although DCIS treated with breast conserving surgery (BCS) has been shown to result in very low mortality rates, the risk of ipsilateral breast tumor recurrence, or IBTR is known to be high, approximately 10–30% at 10 years, without adequate adjuvant treatment such as radiation therapy (RT) or endocrine therapy(5, 6). Therefore, many researchers have tried to assess which factors influence IBTR so as to provide a more individualized adjuvant treatment strategy to prevent IBTR while avoiding the morbidity of treatment itself. Several clinicopathologic factors including age, menopausal status, family history, margin status, nuclear grade, molecular subtype have been reported to be associated with IBTR (5, 7, 8). Besides the tumor itself, a number of studies have also been conducted regarding the effects of the tumor environment on the pathogenesis and prognosis of the tumor (9–15). And in this

endeavor, there have been many attempts to find imaging biomarkers which can reflect the environment of tumor. High mammographic breast density has been reported to be associated with increased risk of breast cancer (16-18). And the breast density change was reported as a predictive surrogate marker for response to adjuvant endocrine therapy in breast cancer (19). Moreover, King et al reported that increased background parenchymal enhancement (BPE) at breast MRI was strongly predictive of breast cancer odds, and treatment with aromatase inhibitors was associated with decrease in BPE (20, 21). Recently, Hattangadi et al. have tried to quantify the characteristics of breast stromal tissue outside the tumor using signal enhancement ratio (SER) analysis on dynamic contrast enhanced (DCE) MRI (22). In the study, they reported that stromal SER could be a potential indicator for response to treatment and for overall outcome in patients with breast cancer.

Nowadays, breast MRI is increasingly used for screening in women at increased risk of breast cancer, pre-operative evaluation, assessment of response to neoadjuvant chemotherapy, and obtaining prognostic information in breast cancer patients (23-33).

Until now, there has been limited data regarding MR imaging features related to IBTR in DCIS patients treated with BCS. The purpose of this study, therefore, was to investigate whether the features on DCE-MRI is associated with IBTR in DCIS patients who have been treated with breast conserving surgery, in special emphasis on the possible imaging parameters which might reflect the environment of tumor.

MATERIALS AND METHODS

Study population

The institutional review board of our hospital approved this retrospective study and waived the requirement for informed consent. Between January 2004 and December 2009, 320 patients with a pathologic diagnosis of pure ductal carcinoma in situ (DCIS) after curative surgery were retrospectively identified through a search of the preoperative breast MRI database in our institution. Among these patients, the study population was selected using the following inclusion criteria. First, preoperative DCE – MRI taken in our hospital had to be available. Second, there must not have been any previous history of breast cancer including both of invasive disease and in situ only disease. Third, the patients should have been treated with breast conserving surgery (BCS). Fourth, at least 2-year follow-up data (mammogrphy, US or MR) had to be available. Twelve patients were excluded as their preoperative MR scans had been taken in outside hospital, two patients were excluded because they had previous history of breast cancer, eighty-eight patients were excluded as they underwent total mastectomy and three patients were excluded due to lack of

sufficient follow-up period. 215 consecutive patients (median age, 47 years; range, 24-74 years) met our inclusion criteria and composed our study population (Fig.1)(Table 1). There were 5 patients with synchronous bilateral DCIS lesions and 210 patients with a unilateral lesion. In the case of bilateral cancers, images of the one side with more dominant lesions were analyzed.

As adjuvant treatment, whole ipsilateral breast irradiation therapy was offered to the patients following BCS. The prescription dose was 50 or 50.4Gy with a daily dose of 1.8-2.0 Gy fractions. A tumor bed boost and regional node irradiation were not used. Twenty one (9.8%, 21/215) patients had not undergone radiation therapy due to the following reasons: (a) denial of the patients (n=10), (b) small size of the lesions which were measured at surgical specimen (less than 1cm) (n=7), (c) surgeon's decision that relatively wide extent of surgery had been done for the lesions (n=4). No patient received adjuvant systemic chemotherapy including trastuzumab. Adjuvant endocrine therapy was added for patients with hormone receptor-positive DCIS in principle. Among 169 patients with hormone receptor-positive tumors, 12 patients (7.1%) had denied to undergo adjuvant endocrine therapy. And although, in principle, adjuvant endocrine therapy was added for

patients with hormone receptor-positive DCIS, one patient with triple negative DCIS and one patient with HER-2 enriched DCIS had undergone adjuvant endocrine therapy.

IBTR is defined as any recurrence of tumor in the ipsilateral breast without evidence of simultaneous distant recurrence which occurred within 4 months after the diagnosis of the first IBTR (34).

Prognostic variables

Age and menopausal status of patients was recorded. Presentation with clinical findings included women with DCIS detected by palpable mass or nipple discharge. The methods of biopsy, i.e. 14G core-needle-biopsy (CNB), 11G vacuum-assisted biopsy, or excisional biopsy, were recorded. Histopathologic data including the tumor size; nuclear grade (low or intermediate/high); the expression status of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER)-2; and margin width were obtained from surgical histopathology reports. ER and PR positivity were defined as the presence of 10% or more positively stained nuclei at 10X magnification. The intensity of the c-erbB-2 staining was scored as 0, 1+, 2+, or 3+. Tumors with a 3+ score were classified as

HER-2 positive, and tumors with a 0 or 1+ score were classified as negative (35). In tumors with a 2+ score, gene amplification using fluorescence in situ hybridization was used to determine the HER-2 status. The ratios of HER-2 gene copies to the centromeric region of chromosome 17 (CEP 17) less than 2.0 were interpreted as normal and ratios of 2.0 or more as amplified (36). The molecular subtype of the tumor was classified into luminal (hormonal receptor-positive and HER2-negative), HER2 enriched (hormonal receptor-negative and HER2-positive) subtypes and triple negative (hormonal receptor-negative and HER2-negative) (37). Margin width was classified as positive/close (<2 mm), or negative. Patients without residual disease in the re-excision specimen were scored as having negative margins (8).In our hospital, the margin width was not quantitatively recorded in the cases for which the pathologists had judged as having clear resection margin at surgical specimens.

MR Imaging Technique

All preoperative MR examinations were performed using a 1.5-T MRI system (Signa; GE Medical Systems, Milwaukee, WI) with a dedicated phased-array breast coil and a subject in the

prone position. After obtaining a transverse localizer image, sagittal fat-suppressed, T2-weighted, fast spin-echo images were obtained (TR/TE, variable from 5500 to 7150/82; 256×160 matrix; field of view: 200 ×200 mm; 1.5-mm slice thickness; no gap). DCE- MR examinations included one pre-contrast and five post-contrast, bilateral sagittal image acquisitions using a fat-suppressed T1-weighted three dimensional fast spoiled gradient echo sequence (TR/TE, 6.5/2.5; matrix 256×160; flip angle-10° ; field of view-200 ×200 mm; 1.5-mm slice thickness; no gap). Gadobenatedimeglumine (Multihance, Bracco Imaging, Milan, Italy) was injected into an ante-cubital vein using an automated injector (Spectris MR, Medrad Europe, Maastricht, Netherlands) at a dose of 0.1 mmol per kilogram of body weight and at a rate of 3 mL/sec. This was followed by a 20-mL saline flush. Five post-contrast image series were obtained at 76, 165, 345, 434, and 583 seconds after contrast administration. For all studies, early subtraction (i.e., first post-contrast images minus pre-contrast images), axial reformatted, and 3D maximum intensity projection images were generated. The mean interval between the MR examination and surgery was 4.4 days (range, 1-29 days).

Image analysis

For qualitative assessment, all MR images were retrospectively assessed in consensus by two radiologists (S. A. K and N. C with 3 and 10 years, respectively, of experience in interpretation of breast MR imaging) who were aware that the patients had a histopathologic diagnosis of DCIS but were blinded to the information regarding IBTR. The information of tumor location was also provided to the reviewers. The maximal diameter of the lesions was measured. And lesions detected with MR imaging were classified according to BI-RADS lexicon for MR imaging, including morphologic and kinetic features(38). The background parenchymal enhancement (BPE) was visually categorized as minimal, mild, moderate, or marked, as performed in a previous study (20), based on the pre-contrast, first post-contrast T1-weighted and subtraction images. They also categorized the amount of fibroglandular tissue (FGT) which was defined as any non-fatty no-cystic breast parenchyma as fatty (<25%), scattered (25-50%), heterogeneously dense (51-75%), or dense (>75% of breast comprised glandular tissue), on the basis of a combination of T2-weighted fat-suppressed imaging and non-enhanced T1-weighted fat-suppressed imaging (20).

As quantitative kinetic parameter, the signal enhancement ratio of the normal appearing parenchyma around the tumor which compares enhancement in their early post-contrast image with enhancement in the delayed post-contrast image was obtained, as performed in a previous study (22). The SER was calculated using the following equation :

$$SER = (S_e - S_p) / (S_d - S_p)$$

Where S_p, S_e, and S_d represent the signal intensity in pre-contrast (before contrast administration), early post-contrast, and delayed post-contrast images, respectively. Regions of interest (ROIs) were placed on the early (at 76 seconds after contrast injection) post-contrast image on a representative sagittal slice showing the largest dimension of the visible enhancing tumor by a radiologist (S. A. K with 3 years of experience in the interpretation of breast MR imaging) as shown in Fig 2. Five ROIs, each with a 5 mm diameter, were placed extending radially from the enhancing tumor edge such that the first ROI was within the margin of the visible tumor and the next four were in the normal-appearing parenchyma. To evaluate the intraobserver variability for the SER measurements, the second set of these ROIs was placed along different direction. And the sets of ROIs were copied and pasted on

the same sagittal slice of delayed (at 583 seconds after contrast injection) post-contrast image as the representative slice of early post-contrast image. The mean SER values from the ROIs in the normal appearing parenchyma of each set were calculated.

To estimate the interobserver variability for the SER quantitative analysis, another radiologist (E. B. R with 2 years of experience in the interpretation of breast MR imaging) also measured the SER for all cases, independently. The ROIs already placed on the images were removed by the research assistant before this process. The values obtained for the parenchymal SER were analyzed for any differences with respect to the observers.

Statistical Analysis

To determine the differences in clinicopathologic and radiologic features according to the IBTR, the independent sample t- test, Chi-square test were used. To determine the optimal cut-off value of SER showing the highest sum of the sensitivity and specificity for differentiating between the IBTR and no IBTR groups, empirical receiver operating characteristic (ROC) analysis was performed.

The primary outcome was recurrence-free survival (RFS). RFS was defined from the date of surgery to the date of IBTR detection at follow-up imaging. Data in patients were censored at the date of most recent follow-up without evidence of disease. Recurrence free survival rates were calculated using the Kaplan-Meier method. The log-rank test was used for univariate comparisons. Cox proportional hazards model was used to analyze the hazard ratio with 95% confidence interval on RFS of clinicopathologic variables (age, menopausal status, clinical presentation, radiation treatment, adjuvant endocrine therapy, methods of biopsy, nuclear grade of tumor, margin width, expressional status of ER, molecular subtype and size of tumor at specimen) and MRI parameters (maximal diameter, BPE, FGT, background parenchymal SER, type of lesion, enhancement kinetics of tumor). Variables with P-values <.1 on univariate analysis were entered as input variables for a multivariate model. Cases with missing data were excluded from the Cox model. For each covariate, the proportional hazard assumption was verified initially by graphic checks, using a log-minus-log survival plot. Formal checks were derived from a test based on time-dependent covariates, and Cox-Snell residuals were used to evaluate the fit of the model. A plot of

the estimated cumulative hazard rate versus Cox-Snell residuals followed a 45° line.

The reproducibility of the SER measurements was evaluated by using the intraclass correlation coefficient (ICC). Inter- and intraobserver agreements were assessed by applying a two-way ICC with random raters assumption and a one-way ICC, respectively. And statistical analyses regarding background SER were performed independently for the values obtained by reader 1 and reader 2.

A two-sided significance level of 5% was used for all analyses. SPSS (version 19.0; SPSS, Chiago, Ill) software was used for all data analysis except the ROC curve analysis, which was performed using MedCalc software (version 10.3.0.0; MedCalc Software, Mariakerke, Belgium).

RESULTS

Patients and Survival Outcome

Of the 215 patients, an IBTR occurred in 15 patients (7.0%) at a median of 36 month (range, 11−61months) period (Table 1) with 9 DCIS and 6 invasive breast cancer patients. Remaining 200 patients did not experience IBTR at a median of 48 month (range, 27−100 months) follow−up. The mean diameter of tumors at the pathologic specimen was 2.90cm ± 1.99cm (range, 0.2cm – 9.8cm). The mean size of the tumor measured as the maximal diameter on MRI was 2.80cm ± 1.75cm (range, 0.4cm – 8.9cm).

Reproducibility for SER measurements, ROC analysis

The ICC values between repeated measurements for mean SER along different directions (intraobserver variability) by reader 1 and reader 2 were 0.889 (95% confidence interval [CI] : 0.857, 0.914; $P<.001$), and 0.875 (95% CI : 0.839, 0.903; P<.001) which indicate excellent agreement, respectively. Because the assessment for intraobserver variability of each reader showed excellent agreement, these data were averaged and used for further analysis. The ICC between the two radiologists (interobserver variability)

was 0.852 (95% CI: 0.811, 0.885; P < .001) for measurements of the SER, which indicates excellent agreement. The area under the ROC curve (A*z*) of the mean SER around tumor obtained by reader 1 and reader 2 were 0.885 (95% CI: 0.817, 0.952, *P*< .001), 0.766 (95% CI: 0.614, 0.917, *P*= .001) for distinguishing the IBTR and no IBTR groups. When the optimal cut-off value of 0.51 was used, the SER quantification showed 80.0% sensitivity and 88.0% specificity by reader 1 and 66.7% sensitivity and 88.5% specificity by reader 2 for distinguishing between the IBTR and no IBTR groups

Survival Analysis: Univariate

The high mean background parenchymal SER around the tumor (HR = 18.359, 95% CI : 5.124, 65.779; *P*< .001, by reader 1, HR = 9.715, 95% CI : 3.274, 28.829 ; *P*<.001, by reader 2), omission of adjuvant endocrine therapy (HR = 3.730, 95% CI : 1.347, 10.327; *P*= .007), omission of radiation therapy (HR = 3.455, 95% CI : 1.092, 10.938; *P*= .025), and plateau or wash - out kinetic pattern of tumor on MRI(HR = 4.541, 95% CI : 1.218, 16.927; *P*= .013), and histologic tumor size (HR = 1.270, 95% CI : 1.016, 1.589, *P* = .036) were significantly associated with early IBTR (Table 2).

There was no significant association between menopausal status (*P*= .133), surgical margin (*P*=.139), initial presentation (*P*=.121), age of patients (*P*=.328), the methods of biopsy (*P*=.319), nuclear grade (*P*= .549), the expression status of ER (*P*= .915), the molecular subtypes of the tumor (*P*= .830) and IBTR.

Among the variables analyzed in MR imaging, the measured longest diameter of lesions (*P*= .541), BPE (*P*= .254), the amount of fibroglandular tissue of breast (*P*= .261), and the type of lesion (mass or non-mass like enhancement)(*P*= .523) were not significant prognostic factors for recurrence free survival in the univariate model. Four variables (the mean SER around tumor, adjuvant endocrine therapy, adjuvant radiation therapy, and the size of tumors measured at specimen) were included in multivariate models.

Survival Analysis: Multivariate

The high mean SER around the tumor (hazard ratio (HR) = 17.873, 95% CI: 4.958, 64.472 ; *P*< .001), omission of the adjuvant endocrine therapy (HR=3.308, 95% CI: 1.152, 9.5 ; *P*= .026) and larger size of tumor measured at surgical specimen (HR=1.316, 95%

CI: 1.061, 1.633 ; *P*= .012) were independent poor prognostic factors for IBTR (Table 3) based on the measurement of mean background parenchymal SER around tumor by reader 1. These factors (The high mean SER [HR = 10.136, 95% CI: 3.392, 30.288; *P*< .001], omission of the adjuvant endocrine therapy [HR=3.202, 95% CI: 1.129, 9.076; *P*= .029] and larger pathologic tumor size [HR=1.382, 95% CI: 1.099, 1.738; *P*= .006]) were also demonstrated as independent prognostic factors for early IBTR on the basis of the measurement of SER by reader 2.

DISCUSSION

In our study, we have demonstrated that the SER of normal appearing background parenchyma around the tumor greater than 0.51 on preoperative MRI was the independent significant predictor for early IBTR in patients with DCIS who had been treated with breast conserving surgery. Among the clinicopathologic characteristics, the omission of the adjuvant endocrine therapy and larger size of tumor measured at surgical specimen were independent poor prognostic factors for IBTR. Our study results indicate that among the MR features of patients with DCIS, the measurement of background SER have the potential to be used as imaging biomarker for IBTR.

The quantification of SER on DCE-MRI has been widely adopted for many researches which focused on the characterization of tumor for the differentiation of malignant from benign pathology, or for the prediction of prognosis of cancer (30, 31, 33, 39). In earlier studies, SER analysis has been found to correlate with tumor angiogenesis as measured histologically by microvessel density (MVD), and have a close correlation with k_{ep}, the well-known imaging parameter representing outflow rate constant on a pixel-

by-pixel basis (40, 41). So the analysis of SER has been supposed to be helpful in the prediction of the clinical outcome of the cancer patient, and has also been investigated for its ability to be used as the surrogate marker to measure the effects of antiangiogenic therapy (30, 31, 42-45). Currently, many researchers turned their eyes from focusing the tumor factor to the microevironment of tumor for the understanding of the cancer pathophysiology. In this endeavor, in a series by Hattangadi et al.(22), they applied SER analysis in characterizing the breast stroma outside the tumor in women with invasive breast cancer, and have demonstrated that background SER was associated with response to neoadjuvant chemotherapy, and therefore could be a potential indicator for response to treatment and for overall outcome in patients with breast cancer. However, there has been limited data regarding the nature of extratumoral angiogenesis and its influence on clinical outcome. In these circumstances, a recent interdisciplinary study of normal-appearing breast tissue have demonstrated that percent enhancement surrounding breast cancer in DCE-MRI was found to be significantly elevated within 2cm of the tumor edge and this region was found to have increased MVD, and genomic changes that were closely associated with host normal breast tissue (46). In

addition, prior studies have indicated that DCIS lesions are capable of inducing a vascular stroma (11). So we adopted the SER analysis of normal-looking parenchyma around the tumor as possible imaging biomarker that has association with clinical outcome of DCIS patients. And our results that the higher SER around tumor was the independent significant predictor for early IBTR in patients with DCIS, were in close agreement with forementioned previous studies.

Omission of adjuvant endocrine treatment was also found to be an independent predictor of IBTR in our study. There have been debates about the benefit of adjuvant endocrine treatment (47, 48). In the NSAPB B24 trial which treated all DCIS patients after BCS with radiotherapy and randomized them to either tamoxifen or placebo group, women in the tamoxifen group were found to have 50% relative risk reduction in all breast cancer events, mainly by reduction in the frequency of ipsilateral invasive cancer recurrence (47). Subsequent retrospective update of NSABP B24 trial suggested that the benefit of tamoxifen was confined to those who had ER-positive DCIS (49). In our hospital, adjuvant endocrine therapy was added for patients with hormone receptor-positive DCIS. However, multivariate analysis for all DCIS patients including

hormone receptor positive and negative tumors together revealed that the omission of adjuvant endocrine therapy is poor prognostic factor for recurrence free survival. We suppose that the strong influence of endocrine treatment on risk of IBTR and the composition of our cohort in which majority of tumors belonged to hormone receptor positive tumor (78.6%, 169/215) have brought this result. We also found that larger size of tumor measured at surgical specimen was an independent poor prognostic factor for IBTR. This result corresponds to previous studies on prognostic index which combined tumor size with margin width and pathologic classification as variables for decision for adjuvant treatment in DCIS patients (50).

Furthermore, among the MR features, plateau or wash-out pattern of enhancement kinetics of tumor (P= .013) was associated with early IBTR in univariate analysis. This factor was not included in multivariate analysis, because we could not analyze the enhancement kinetics of tumor in 57 patients (26.7% of total patients) who had undergone excisional biopsy. To our knowledge, there have been limited data regarding the association of enhancement kinetics of tumor with the IBTR of DCIS whereas wash-out pattern of enhancement kinetics of tumor in IDC is known

to be correlated with clinical outcome of patients, and many researches using quantitative parameters have been conducted to prove it (30, 31, 43). The enhancement kinetics of invasive lesions typically show a rapid increase and a washout over time, while benign lesions tend to enhance more slowly and persistently take up contrast medium over time (39). DCIS lesions have been found to have less suspicious kinetic findings, i.e. plateau or persistent enhancement curves, more frequently compared with invasive cancers (51). Various reports have been made on the correlation of kinetic characteristics with the histologic grade of DCIS, but sufficient conclusion was not come to (33, 51). So, there should be further future study regarding association of the enhancement kinetics of DCIS with the prognosis of patients.

Our study has an advantage in that we could have included our study cohort from the consecutive large preoperative database of breast cancer patients who had undergone curative surgery. Additionally, in our hospital, nearly all patients with breast cancer have undergone preoperative DCE-MRI except those who have underlying diseases which are contraindicated by the use of gadolinium based contrast agents. Although our study design was the retrospective analysis, by using this consecutive database, we

could minimize the selection bias of patients.

However, there are some limitations to our study. First, the measurement of background SER around the tumor may be somewhat subjective, as the placement of ROIs and the choice of representative slice might have affected the results. To overcome this variability issue, we have conducted repeated measurement of SER by two radiologists. The ICC between repeated measurements for mean SER along different directions by one radiologist and the ICC between two radiologists for mean SER indicate excellent agreement. In addition, when we analyzed the recurrence free survival of patients using the mean SER value independently measured by two radiologists, we could observe same result repeatedly that background SER around tumor associated with the IBTR in DCIS patients. Although our method for analysis of SER has an strength in that it is semi-quantative, and relatively easy to use in clinical setting, an objective method for SER quantification such as a computer-aided SER mapping should be considered in future studies. Second, the MRI examination was not scheduled according to the patient's menstrual cycle. It has been shown in previous study that parenchymal enhancement on breast MRI might be variable according to the menopausal status and menstrual

cycle(52). However, recently, Katrin H. et al have reported that the associations between contrast enhancement kinetics of normal breast parenchyma and the menstrual cycle was negligible in their prospective population based study which included 345 DCE MR data sets. Third, the dichotomized cut-off value of SER was obtained from our study population. So its predictive power for the IBTR could have been overestimated. But, Az value obtained in our study was relatively high (0.885 [95% CI: 0.817, 0.952, P< .001]by reader 1, 0.766 [95% CI: 0.614, 0.917, P= .001]) by reader 2), and hazard ratio calculated using this value was 17.873 (95% CI: 4.958, 64.472 ; P< .001) and 10.136 (95% CI: 3.392, 30.288; P< .001), by reader 1 and reader 2, respectively. Therefore, even if the predictive power had been overestimated, we believe that our results might be statistically meaningful.

In conclusion, a higher background parenchymal SER around tumor measured in pre-operative DCE-MR was found to be an independently significant predictor for early IBTR in DCIS patients treated with BCS. Among other MR features, enhancement kinetics of tumor appeared to be correlated with the IBTR of patients with DCIS. And we also found that omission of adjuvant endocrine treatment and large extent of tumor measured at surgical specimens

are independent factors associated with subsequent IBTR. Therefore, the parenchymal SER analysis on pre-operative DCE-MRI can aid in predicting the prognosis of patients with DCIS who considering BCS as their curative surgery.

Tables

Table 1. Characteristics of 215 DCIS Patients Treated with BCS

Characteristics	Total (n=215)	IBTR (n=15)	No IBTR (n=200)	*P*
Age at surgery				
<45	76 (35.3)	7 (46.7)	69 (34.5)	.404
≥45	139 (64.7)	8 (53.3)	131 (65.5)	
Menopausal status				
Pre/peri	149(69.3)	13 (86.7)	136 (68.0)	.157
Post	66 (30.7)	2 (13.3)	64 (32.0)	
Clinical presentation				
Clinical	53 (24.7)	6 (40.0)	47 (23.5)	.210
Radiologic	162 (75.3)	9 (60.0)	153 (76.5)	
Radiation therapy				
No	21 (9.8)	4 (26.7)	17 (8.5)	.045
Yes	194 (90.2)	11 (73.3)	183 (91.5)	
Endocrine therapy				
No	56 (26.0)	8 (53.3)	48 (24.0)	.018
Yes	159(74.0)	7 (46.7)	152 (76.0)	
Nuclear grade				
Intermediate/High	120 (55.8)	7 (46.7)	113 (56.5)	.592
Low	95 (44.2)	8 (53.3)	87 (43.5)	
Margin				
Close/Positive	39 (18.1)	5 (33.3)	34 (17.0)	.156
Negative	176 (81.9)	10 (66.7)	166 (83.0)	
Methods of biopsy				
14G gun	84 (39.1)	5 (33.3)	79 (39.5)	.467
11G vacuum	74 (34.4)	4 (26.7)	70 (35.0)	
Excision	57 (26.5)	6 (40.0)	51 (25.5)	
ER status				
Positive	156 (72.6)	11 (73.3)	145 (72.5)	1.000
Negative	59 (27.4)	4 (26.7)	55 (27.5)	
Subtype				
Luminal	169 (78.6)	12 (80.0)	157 (78.5)	.838
HER2 enriched	23 (10.7)	1 (6.7)	22 (11.0)	
TPN	23 (10.7)	2 (13.3)	21 (10.5)	
Histologic tumor size[a]	2.90±1.99	3.91±2.13	2.83±1.97	.074

Tumor size at MR[a]	2.80±1.75	2.39±1.08	2.79±1.78	.325

Note.—Values are numbers of patients with percentages calculated on the basis of the each group in parentheses, except where otherwise specified. DCIS = ductal carcinoma in situ, BCS = breast conserving surgery, IBTR = ipsilateral breast tumor recurrence, TPN = triple negative

[a] Values are the mean ± standard deviation (cm).

Table 2. Univariate association between prognostic variables and IBTR

Characteristics	Number (n=215)	IBTR (n=15)	HR	95% CI	*P*
Age at surgery					
< 45	76(35.3)	7 (46.7)	1.652	0.598,4.563	.328
≥ 45	139(64.7)	8 (53.3)	1		
Menopause					
Pre/peri	149(69.3)	13(86.7)	2.964	0.669,13.138	.133
Post	66(30.7)	2 (13.3)	1		
Presentation					
Clinical	53(24.7)	6 (40.0)	2.271	0.806, 6.399	.121
Radiologic	162(75.3)	9 (60.0)	1		
Radiation therapy					
No	21(9.8)	4 (26.7)	3.455	1.092,10.938	.025
Yes	194(90.2)	11(73.3)	1		
Endocrine therapy					
No	56 (26.0)	8 (53.3)	3.730	1.347,10.327	.007
Yes	159(74.0)	7 (46.7)	1		
Nuclear grade					
Intermediate/ High	120(55.8)	7 (46.7)	0.734	0.266, 2.027	.549
Low	95(44.2)	8 (53.3)	1		
Margin					
Close/Positive	39(18.1)	5 (33.3)	2.204	0.753, 6.451	.139
Negative	176(81.9)	10(66.7)	1		
Methods of biopsy					
Excision	57(26.5)	6 (40.0)	1.952	0.593, 6.419	.319
11G vacuum	74(34.4)	4 (26.7)	0.805	0.216, 3.006	
14G gun	84(39.1)	5 (33.3)	1		
ER status					
Positive	156(72.6)	11(73.3)	1.064	0.338, 3.351	.915
Negative	59(27.4)	4 (26.7)	1		
Subtype					
Luminal	169(78.6)	12(80.0)	1		.830
HER2 enriched	23(10.7)	1(6.7)	0.650	0.085, 5.005	
TPN	23(10.7)	2 (13.3)	1.356	0.301, 6.104	
Histologic tumor size[a] (cm)	2.90 ± 1.99	3.91 ± 2.13	1.270	1.016,1.589	.036
Tumor size at MR[a,b] (cm)	2.80 ±1.75	2.39 ±1.08	.875	0.570, 1.343	.541

BPE[c]					
Non/Minimal	36(16.7)	1(6.7)	1		.254
Mild	74(34.4)	4(26.7)			
Moderate	60(27.9)	4(26.7)	1.855	0.632, 5.447	
Marked	45(20.9)	6(40.0)			
FGT[c]					
Fatty	5(2.3)	0(0.0)	1		.261
Scattered	47(21.9)	2(13.3)			
Heterogenously −dense	81(37.7)	6(40.0)	2.300	0.517,10.237	
Dense	82(38.1)	7(46.7)			
Parenchymal SER					
Reader 1					
> 0.51	36 (16.7)	12(80.0)	18.359	5.124,65.779	<.001
≤0.51	179(83.3)	3(20.0)	1		
Reader 2					
> 0.51	33 (15.3)	10(66.7)	9.715	3.274,28.829	<.001
≤0.51	182(84.7)	5 (33.3)	1		
Lesion type[b]					
Mass	21(13.3)	2 (22.2)	1.663	0.344, 8.039	.523
NMLE	137(86.7)	7 (77.8)	1		
Lesion kinetics[b, d]					
Wash−out	8(5.1)	1(11.1)	4.541	1.218,16.927	.013
Plateau	26(16.5)	4(44.4)			
Persistent	124(78.5)	4(44.4)	1		

Note.—Values in parentheses are percentages calculated on the basis of the each group. IBTR = ipsilateral breast tumor recurrence, HR = hazard ratio, 95% CI = 95% confidence interval for hazard ratio, TPN = triple negative, BPE = background parenchymal enhancement, FGT = fibroglandular tissue density, SER = signal enhancement ratio, NMLE = non−mass like enhancement.

[a] Values are the mean ± standard deviation (cm).

[b]Data was obtained from the patients who had not undergone excisional biopsy before MR examination

[c]Lower two categories and higher two categories of the four-point scales of BPE and FGT were combined for the analysis of HR, CI and P-value

[d] Wash-out and plateau patterns were combined for the analysis of HR, CI, and P-value

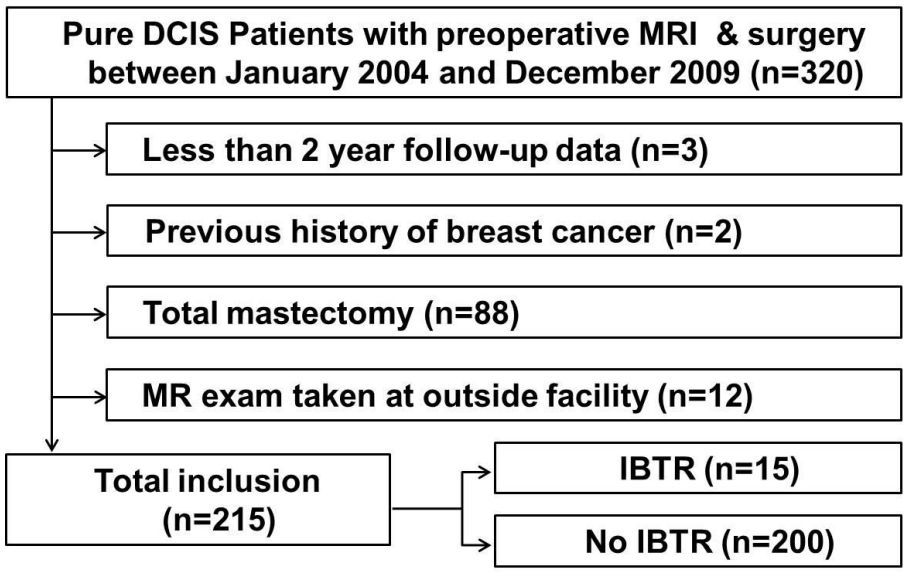
Table 3. Multivariate models of prognostic variables associated with IBTR

Characteristics	HR		*P*	
	Reader 1	Reader 2	Reader1	Reader2
Radiation therapy				
No	2.040	2.547	.254	.134
Yes	1	1		
Endocrine therapy				
No	3.308	3.202	.026	.029
Yes	1	1		
Size of Tumor at specimen[a]	1.316	1.382	.012	.006
Parenchymal SER				
> 0.51	17.873	10.136	<.001	<.001
≤ 0.51	1	1		

Note.— IBTR = ipsilateral breast tumor recurrence, HR = hazard ratio, SER = signal enhancement ratio

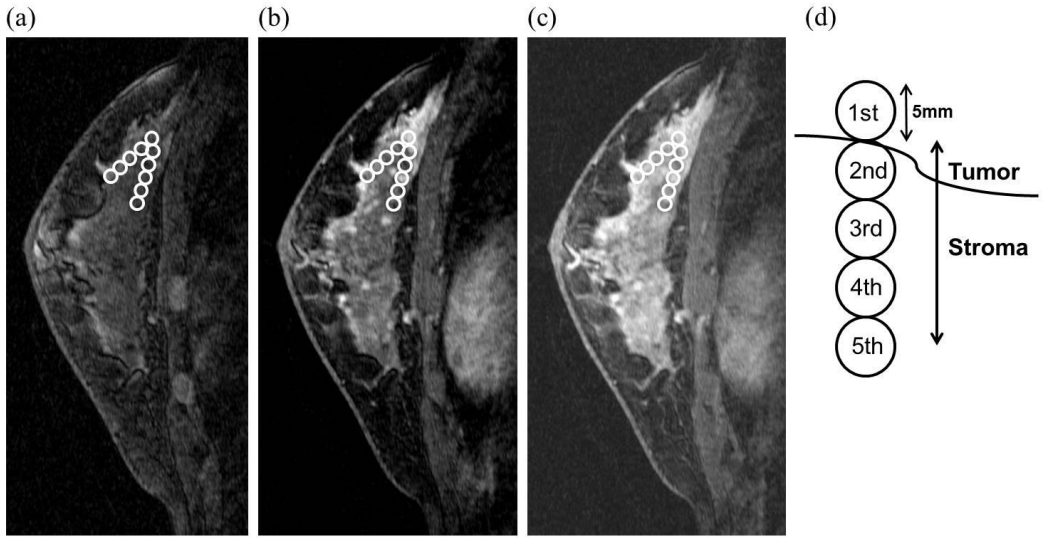
Figures

Figure 1. Flow chart shows the study population selection.



Note. — DCIS = ductal carcinoma in situ, IBTR = ipsilateral breast tumor recurrence

Figure 2. A representative case of the IBTR group ; A 42-year-old woman with DCIS whose disease relapsed at ipsilateral breast 37months after surgery.

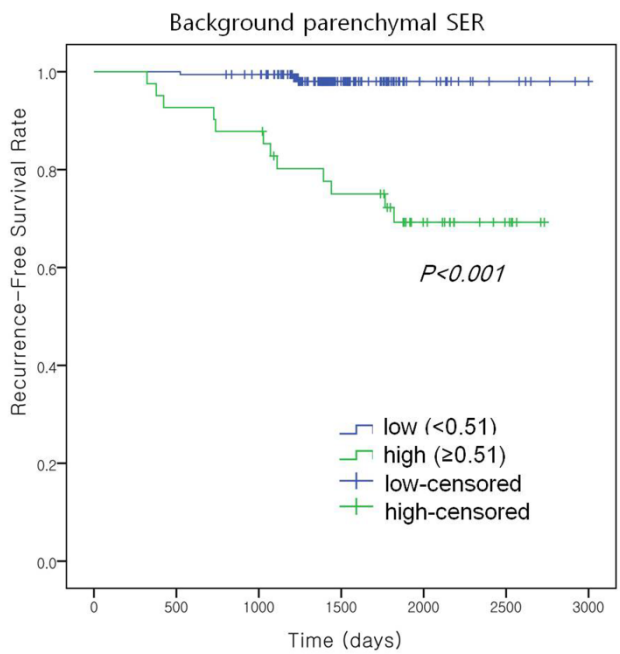


Two sets of five circular regions of interest (ROI) were placed extending radially from the tumor edge in the same locations on the (a) pre-contrast, (b) early post-contrast and (c) delayed post-contrast phases. Each ROI is 5mm in diameter. On the (d) schematic diagram, the first ROI of each set was placed just within the visible tumor and next four ROIs were placed in normal-appearing background stroma. (e) The example of calculation of mean SER. The signal enhancement ratio of second ROI (ROI^{2nd}) was measured using following equation. $SER(ROI^{2nd}) = [S_e(ROI^{2nd})$

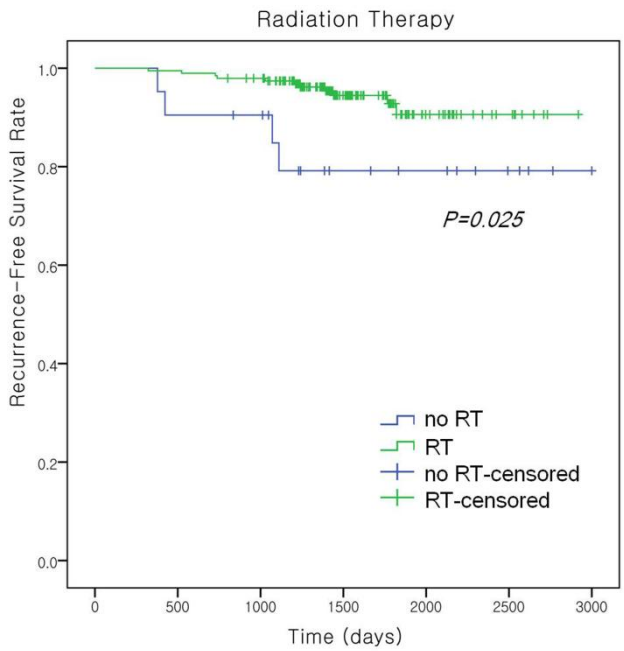
$- S_p(ROI^{2nd})] / [S_d(ROI^{2nd}) - S_p(ROI^{2nd})]$, where $S_p(ROI^{2nd})$, $S_e(ROI^{2nd})$, and $S_d(ROI^{2nd})$ represent the signal intensity measured at second ROI in the pre-contrast, early post-contrast, and delayed post-contrast images, respectively. The third, fourth, and fifth SER were calculated using same equation. And then, the mean SER from the four ROIs was calculated. In this case the mean SER of normal-appearing background stroma around tumor was 0.67.

Figure 3. Kaplan–Meier curves demonstrating association between prognostic variables on IBTR. Association of (a) mean SER of normal–appearing background parenchyma around tumor measured by reader 1 (>0.51, ≤ 0.51), (b)radiation therapy, (c) adjuvant endocrine therapy, and (d) enhancement kinetics of tumor[a] (wash–out or plateau, persistent). The *p*–value was calculated using the log rank test.

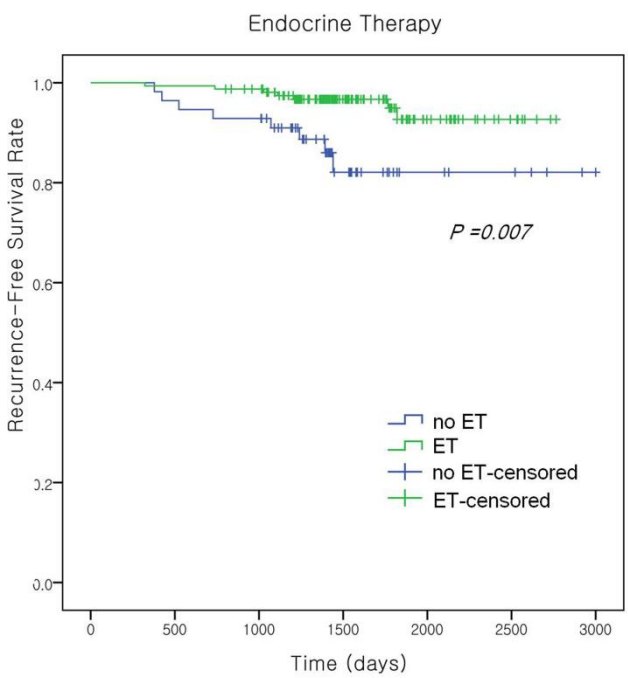
(a)



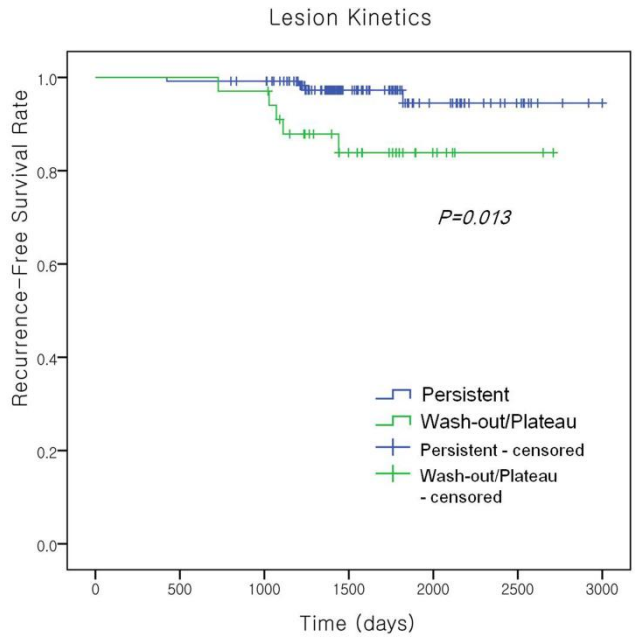
(b)


Radiation Therapy
Recurrence-Free Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.025
no RT
RT
no RT-censored
RT-censored
0
500
1000
1500
2000
2500
3000
Time (days)

(c)


Endocrine Therapy
Recurrence-Free Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
P =0.007
no ET
ET
no ET-censored
ET-censored
0
500
1000
1500
2000
2500
3000
Time (days)

(d)



Note. —

[a] Data was obtained from the patients who had not undergone excisional biopsy before MR examination. SER = signal enhancement ratio, RT = radiation therapy, ET = endocrine therapy

References

1. Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. Journal of the National Cancer Institute. 2002;94(20):1546-54.

2. Kumar AS, Bhatia V, Henderson IC. Overdiagnosis and overtreatment of breast cancer: rates of ductal carcinoma in situ: a US perspective. Breast cancer research : BCR. 2005;7(6):271-5.

3. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA: a cancer journal for clinicians. 2011;61(6):409-18.

4. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA: a cancer journal for clinicians. 2011;61(4):212-36.

5. Group EBCC, Group ER, Bijker N, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC

Radiotherapy Group. J Clin Oncol. 2006;24(21):3381-7.

6. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J Clin Oncol. 2008;26(8):1247-52.

7. Hiramatsu H, Bornstein BA, Recht A, et al. Local recurrence after conservative surgery and radiation therapy for ductal carcinoma in situ: Possible importance of family history. The cancer journal from Scientific American. 1995;1(1):55-61.

8. Rudloff U, Jacks LM, Goldberg JI, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol. 2010;28(23):3762-9.

9. Bailey KM, Wojtkowiak JW, Hashim AI, Gillies RJ. Targeting the metabolic microenvironment of tumors. Advances in pharmacology. 2012;65:63-107.

10. Friedl P, Alexander S. Cancer invasion and the microenvironment: plasticity and reciprocity. Cell. 2011;147(5):992-1009.

11. Guidi AJ, Schnitt SJ, Fischer L, et al. Vascular permeability factor (vascular endothelial growth factor) expression and

angiogenesis in patients with ductal carcinoma in situ of the breast. Cancer. 1997;80(10):1945-53.

12. Kim BG, An HJ, Kang S, et al. Laminin-332-rich tumor microenvironment for tumor invasion in the interface zone of breast cancer. The American journal of pathology. 2011;178(1):373-81.

13. Monsky WL, Mouta Carreira C, Tsuzuki Y, Gohongi T, Fukumura D, Jain RK. Role of host microenvironment in angiogenesis and microvascular functions in human breast cancer xenografts: mammary fat pad versus cranial tumors. Clinical cancer research : an official journal of the American Association for Cancer Research. 2002;8(4):1008-13.

14. Straussman R, Morikawa T, Shee K, et al. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. Nature. 2012;487(7408):500-4.

15. Weaver VM, Fischer AH, Peterson OW, Bissell MJ. The importance of the microenvironment in breast cancer progression: recapitulation of mammary tumorigenesis using a unique human mammary epithelial cell model and a three-dimensional culture assay. Biochemistry and cell biology = Biochimie et biologie cellulaire. 1996;74(6):833-51.

16. Jeon JH, Kang JH, Kim Y, et al. Reproductive and Hormonal

Factors Associated with Fatty or Dense Breast Patterns among Korean Women. Cancer research and treatment : official journal of Korean Cancer Association. 2011;43(1):42-8.

17. Mousa NA, Crystal P, Wolfman WL, Bedaiwy MA, Casper RF. Aromatase inhibitors and mammographic breast density in postmenopausal women receiving hormone therapy. Menopause. 2008;15(5):875-84.

18. Park CC, Rembert J, Chew K, Moore D, Kerlikowske K. High mammographic breast density is independent predictor of local but not distant recurrence after lumpectomy and radiotherapy for invasive breast cancer. International journal of radiation oncology, biology, physics. 2009;73(1):75-9.

19. Kim J, Han W, Moon HG, et al. Breast density change as a predictive surrogate for response to adjuvant endocrine therapy in hormone receptor positive breast cancer. Breast cancer research : BCR. 2012;14(4):R102.

20. King V, Brooks JD, Bernstein JL, Reiner AS, Pike MC, Morris EA. Background parenchymal enhancement at breast MR imaging and breast cancer risk. Radiology. 2011;260(1):50-60.

21. King V, Goldfarb SB, Brooks JD, et al. Effect of Aromatase Inhibitors on Background Parenchymal Enhancement and Amount of

Fibroglandular Tissue at Breast MR Imaging. Radiology. 2012;264(3):670-8.

22. Hattangadi J, Park C, Rembert J, et al. Breast stromal enhancement on MRI is associated with response to neoadjuvant chemotherapy. AJR American journal of roentgenology. 2008;190(6):1630-6.

23. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology. 2004;233(3):830-49.

24. Friedlander LC, Roth SO, Gavenonis SC. Results of MR imaging screening for breast cancer in high-risk patients with lobular carcinoma in situ. Radiology. 2011;261(2):421-7.

25. Lee JM, McMahon PM, Kong CY, et al. Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. Radiology. 2010;254(3):793-800.

26. Morrow M, Waters J, Morris E. MRI for breast cancer screening, diagnosis, and treatment. Lancet. 2011;378(9805):1804-11.

27. Sung JS, Lee CH, Morris EA, Oeffinger KC, Dershaw DD. Screening breast MR imaging in women with a history of chest

irradiation. Radiology. 2011;259(1):65-71.

28. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. 2010;375(9714):563-71.

29. Iima M, Le Bihan D, Okumura R, et al. Apparent diffusion coefficient as an MR imaging biomarker of low-risk ductal carcinoma in situ: a pilot study. Radiology. 2011;260(2):364-72.

30. Li KL, Partridge SC, Joe BN, et al. Invasive breast cancer: predicting disease recurrence by using high-spatial-resolution signal enhancement ratio imaging. Radiology. 2008;248(1):79-87.

31. Li SP, Makris A, Beresford MJ, et al. Use of dynamic contrast-enhanced MR imaging to predict survival in patients with primary breast cancer undergoing neoadjuvant chemotherapy. Radiology. 2011;260(1):68-78.

32. Park SH, Moon WK, Cho N, et al. Diffusion-weighted MR imaging: pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. Radiology. 2010;257(1):56-63.

33. Rahbar H, Partridge SC, Demartini WB, et al. In vivo assessment of ductal carcinoma in situ grade: a model incorporating dynamic contrast-enhanced and diffusion-weighted breast MR

imaging parameters. Radiology. 2012;263(2):374-82.

34. Taghian A, Jeong JH, Mamounas E, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. J Clin Oncol. 2004;22(21):4247-54.

35. Rhee J, Han SW, Oh DY, et al. The clinicopathologic characteristics and prognostic significance of triple-negativity in node-negative breast cancer. BMC Cancer. 2008;8:307.

36. Dolan M, Snover D. Comparison of immunohistochemical and fluorescence in situ hybridization assessment of HER-2 status in routine practice. Am J Clin Pathol. 2005;123(5):766-70.

37. Fumagalli D, Bedard PL, Nahleh Z, et al. A common language in neoadjuvant breast cancer clinical trials: proposals for standard definitions and endpoints. The lancet oncology. 2012;13(6):e240-8.

38. (ACR) ACoR. BI-RADS : Magnetic Resonance Imaging. Reston, Va: American College of Radiology, 2003: 1-109.

39. Bhooshan N, Giger ML, Jansen SA, Li H, Lan L, Newstead GM. Cancerous breast lesions on dynamic contrast-enhanced MR images: computerized characterization for image-based prognostic

markers. Radiology. 2010;254(3):680-90.

40. Esserman L, Hylton N, George T, Weidner N. Contrast-Enhanced Magnetic Resonance Imaging to Assess Tumor Histopathology and Angiogenesis in Breast Carcinoma. The breast journal. 1999;5(1):13-21.

41. Li KL, Henry RG, Wilmes LJ, et al. Kinetic assessment of breast tumors using high spatial resolution signal enhancement ratio (SER) imaging. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 2007;58(3):572-81.

42. Fujimoto K, Abe T, Muller NL, et al. Small peripheral pulmonary carcinomas evaluated with dynamic MR imaging: correlation with tumor vascularity and prognosis. Radiology. 2003;227(3):786-93.

43. Hylton N. Dynamic contrast-enhanced magnetic resonance imaging as an imaging biomarker. J Clin Oncol. 2006;24(20):3293-8.

44. Schlemmer HP, Merkle J, Grobholz R, et al. Can pre-operative contrast-enhanced dynamic MR imaging for prostate cancer predict microvessel density in prostatectomy specimens? European radiology. 2004;14(2):309-17.

45. Tuncbilek N, Unlu E, Karakas HM, Cakir B, Ozyilmaz F. Evaluation of tumor angiogenesis with contrast-enhanced dynamic magnetic resonance mammography. The breast journal. 2003;9(5):403-8.

46. Nabavizadeh N, Klifa C, Newitt D, et al. Topographic enhancement mapping of the cancer-associated breast stroma using breast MRI. Integrative biology : quantitative biosciences from nano to macro. 2011;3(4):490-6.

47. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet. 1999;353(9169):1993-2000.

48. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet. 2003;362(9378):95-102.

49. Allred DC BJ, Land S, Paik S, Fisher E, Julian T, Margolese R, Smith R, Mamounas T, Osborne CK, Fisher B, Wolmark N. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from the NSABP Protocol B-24. Breast cancer research and treatment.

2002;76 Suppl 1:S29-180.

50. Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. American journal of surgery. 2003;186(4):337-43.

51. Jansen SA, Newstead GM, Abe H, Shimauchi A, Schmidt RA, Karczmar GS. Pure ductal carcinoma in situ: kinetic and morphologic MR characteristics compared with mammographic appearance and nuclear grade. Radiology. 2007;245(3):684-91.

52. Muller-Schimpfle M, Ohmenhauser K, Stoll P, Dietz K, Claussen CD. Menstrual cycle and age: influence on parenchymal contrast medium enhancement in MR imaging of the breast. Radiology. 1997;203(1):145-9.

요약(국문초록)

관내상피암의 유방보존술 후 국소재발암 발생 예측을 위한 종양주변실질의 역동자기공명영상 조영증가율 평가

연구목적 : 유방의 관내 상피암으로 유방 보존술을 시행받은 후 발생한 동측 유방의 국소 재발을 예측하는데 있어서 수술 전 자기 공명 영상에서 측정한 종양 주변 실질의 조영 증가율의 유용성을 후향적으로 평가하고자 하였다.

연구 대상 및 방법 : 2004년부터 2009년까지 관내상피암으로 유방보존술을 시행 받은 환자 중 술전 유방 자기 공명 영상을 시행하였으며 2년 이상의 추적 관찰자료가 있는 215명 (중도 연령, 47세; 범위, 24-74세)의 연속적 환자를 대상으로 하였다. 임상 병리적 자료로 수술 당시의 나이, 폐경 여부, 보조치료 시행 여부, 종양 크기, 호르몬 수용체 상태, 핵의 등급, 외과적 절제연 등을 분석하였으며 자기 공명 영상에서 종양의 특징은 Breast Imaging Reporting and Data System (BI-RADS)어휘편에 따라서 그 형태와 조영 증강 양상을 분류하였고, 영상에서 구할 수

있는 양적 지표로 종양주변 실질의 조영 증가 정도를 평가하였다. 조영 증강 정도는 $(S_e-S_p)/(S_d-S_p)$로 정의되며 여기서 S_p는 조영 전 영상에서의 신호강도, S_e는 초기 조영 후 영상에서의 신호강도, S_d는 지연기 조영 후 영상에서의 신호강도를 뜻한다. 수신자 특성화 곡선이 동측 유방 국소 재발 예측을 위한 조영 증가율의 최적기준치를 정하기 위하여 사용되었다. 조영 증가율 측정의 재현성을 평가하기 위하여 2명의 영상의학과 의사가 독립적으로 증가율을 계산하였으며 분석 방법으로 급내 상관계수가 이용되었다. 무병 생존률이 Kaplan-Meier 법을 사용하여 측정되었으며 다변량 생존분석을 위하여 다변량 Cox 비례 위험모형을 사용하였다.

결과 : 전체 215명 중 15명(7.0%)에서 동측재발이 발생하였고,총 9 명의 환자에서 관상피내암으로 재발하였으며 6명에서 침습성 유방암의 형태로 재발하였다. 조영 증가율 반복측정의 급내 상관 계수는 0.852 (95% 신뢰구간 0.811, 0.985; $P<.001$)로 강한 상관관계를 보였다. 다변량 생존분석에서 높은 종양 주변 실질 조영증가율은 동측 유방 재발에 영향을 미치는 유의한 인자로 분석되었다. 측정된 위험비는 관측자 1이 측정한 값에서는 17.837 (95% 신뢰구간 : 4.958, 64.472 ; $P<.001$) 관측자 2가 측정한 값에서는 10.136 (95% 신뢰구간 : 3.392, 30.288 ; $P<.001$) 이었다. 이외에 보조적 호르몬 치료를 받지 않은 군에서 유의하게 높은 동측 유방 재발을 보였으며 수술 검체에서 측정한 종양의 크

기가 클수록 동측 유방 재발이 유의하게 높았다

결론 :유방의 관내 상피암으로 유방 보존술을 시행받은 후 발생한 동측 유방의 재발에 있어서 수술 전 자기 공명 영상에서 측정한 종양 주변 실질의 조영 증강율과 보조적 호르몬 치료의 생략, 큰 종양의 범위는 유의한 예측인자이다.

주요어 :유방, 자기 공명 영상, 조영 증강 정도, 관내 상피암, 재발, 생존 분석, 유방 실질

학번: 2011-21826