Magn Reson Med Sci, Vol. 12, No. 3, pp. 193–199, 2013
doi:10.2463/mrms.2012-0095


**MAJOR PAPER**

# Correlations between Apparent Diffusion Coefficient Values and Prognostic Factors of Breast Cancer

Takeshi KAMITANI[1]*, Yoshio MATSUO[1], Hidetake YABUUCHI[2], Nobuhiro FUJITA[1], Michinobu NAGAO[3], Mikako JINNOUCHI[1], Masato YONEZAWA[1], Yuzo YAMASAKI[1], Eriko TOKUNAGA[4], Makoto KUBO[5], Hidetaka YAMAMOTO[6], Takashi YOSHIURA[1], and Hiroshi HONDA[1]

[1]*Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University 3–1–1, Maidashi, Higashi-ku, Fukuoka, 812–8582, Japan*
[2–6]*Departments of* [2]*Health Sciences,* [3]*Molecular Imaging and Diagnosis,* [4]*Surgery and Science,* [5]*Surgery and Oncology, and* [6]*Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University*
(Received December 25, 2012; Accepted January 30, 2013; published online July 12, 2013)

Purpose: We investigated possible correlations between apparent diffusion coefficient (ADC) values and prognostic factors of breast cancer.

Methods: We retrospectively evaluated 81 patients who underwent magnetic resonance (MR) imaging of the breast and were diagnosed pathologically with invasive ductal carcinoma (IDC) not otherwise specified with invasive foci one cm or larger. We excluded ductal carcinoma *in situ* and IDC with invasive foci smaller than one cm because small lesions decrease the reliability of signal intensity of diffusion-weighted imaging (DWI). We also excluded special type cancers. We used t-test to compare the mean ADC values of cancers of Stage pT1 ($\leq 2$ cm) versus pT2 or 3 ($>2$ cm), cancers with versus without vascular invasion, axillary lymph node (N)-positive versus N-negative cancers, estrogen receptor (ER)-positive versus ER-negative cancers, and progesterone receptor (PgR)-positive versus PgR-negative cancers. We analyzed correlations between the ADC value with nuclear grade (NG) and human epidermal growth factor receptor 2 (HER2) score by rank test using Spearman's correlation coefficient.

Results: The mean ADC value was significantly higher for N-positive (n = 28; $0.97 \pm 0.20 \times 10^{-3}$ mm$^2$/s) than N-negative cancers (n = 53; $0.87 \pm 0.17 \times 10^{-3}$ mm$^2$/s) ($P = 0.017$); significantly lower for ER-positive (n = 63; $0.88 \pm 0.15 \times 10^{-3}$ mm$^2$/s) than ER-negative cancers (n = 18; $1.01 \pm 0.21 \times 10^{-3}$ mm$^2$/s) ($P = 0.005$); and significantly lower for PgR-positive (n = 47; $0.88 \pm 0.16 \times 10^{-3}$ mm$^2$/s) than PgR-negative cancers (n = 34; $0.95 \pm 0.18 \times 10^{-3}$ mm$^2$/s) ($P = 0.048$). Tumor size, vascular invasion, NG, and HER2 status showed no significant correlation with ADC values.

Conclusion: ADC values were higher for N-positive and ER-negative breast cancers than N-negative and ER-positive cancers.

**Keywords:** *ADC, breast cancer, prognostic factor*

## Introduction

Prognostic risk factors in patients with breast cancer are axillary lymph node (N)-positive status, larger tumor size ($>2$ cm), high nuclear grade (NG), presence of peritumoral vascular invasion, overexpression of human epidermal growth factor receptor type 2 (HER2), and younger age ($<35$).[1] In addition, N status greatly influences choice of operative procedure (sentinel lymph node biopsy [SLNB] or axillary dissection [Ax]) and the decision to administer neoadjuvant chemotherapy. Hormone receptor and HER2 expressions are also im-

*Corresponding author, Phone: +81-92-642-5695, Fax: +81-92-642-5708, E-mail: kamitani@radiol.med.kyushu-u.ac.jp

portant factors in choosing treatment. Although some authors have correlated these factors with findings of dynamic magnetic resonance (MR) imaging,[2–5] we believe only a few studies have reported correlations with apparent diffusion coefficient (ADC) value.

Many reports have described the usefulness of both diffusion-weighted MR imaging (DWI) and ADC value for evaluating primary breast lesions.[6–10] DWI is now widely used in routine clinical MR imaging studies. However, DWI and ADC value have been used mainly to differentiate benign and malignant lesions; only a few reports address correlations between ADC value and prognostic factors.

We therefore investigated possible correlations between ADC values and prognostic factors of breast cancer.

## Materials and Methods

*Patients*

Our institutional committee on clinical study approved this retrospective study, and informed consent was waived. We enrolled 130 consecutive patients who underwent MR imaging of the breast including DWI at our institute between May 1, 2006 and May 31, 2007 who were subsequently proven histopathologically to have breast cancer. We excluded 49 patients, including 25 with ductal carcinoma *in situ* (DCIS) or invasive ductal carcinoma (IDC) with invasive foci of less than one cm (because of the poor reliability of the signal intensity of the ADC map with slightly low spatial resolution), 13 who received neoadjuvant chemotherapy or endocrine therapy, 6 with special type cancer (mucinous carcinoma, 3; invasive lobular carcinoma, 2; metaplastic carcinoma, 1), 4 patients for whom axillary lymph nodes were not sampled, and one patient with low image quality of DWI. As a result, we included 81 patients with 81 breast cancers with invasive foci of one cm or more in this study. All patients were female and aged 34 to 82 years (mean age, 54.3 years). The numbers of cancers by pathological stage were: pT1, 58 (T1b, 4; T1c, 54); pT2, 22; and pT3, one (Union for International Cancer Control [UICC] 2002). Forty cancers were diagnosed as negative for lymph node metastasis by SLNB and 13, by Ax. The remaining 28 cancers were diagnosed as positive for lymph node metastasis; four underwent only SLNB, 15 underwent SLNB followed by Ax, and nine underwent Ax.

*MR imaging*

Patients underwent MR imaging in prone position using a 1.5-tesla system (Intera Achieva Nova Dual, Philips Medical Systems, Best, The Netherlands) with body coil. Axial DWIs of both breasts were obtained at b values of 0, 500, and 1000 s/mm$^2$ with parameters: repetition time (TR), 4600 to 6800 ms; echo time (TE), 51.0 ms; number of excitations (NEX) 2; flip angle, 90°; field of view (FOV), 360 × 360 mm; matrix, 128 × 88; slice thickness, 5.0 mm; slice gap, 1.5 mm. Fat suppression was applied using a spectral attenuated inversion recovery (SPAIR) technique. ADC maps were automatically generated on the operating console by the methods of least squares using all 3 images with b values of 0, 500 and 1000 s/mm$^2$. We placed regions of interest (ROI), maximum-sized circles, within the primary lesions on the ADC maps and obtained ADC values, avoiding apparent necrotic or cystic components by referring to other MR images. Figures 1 to 3 show representative MR images.

*Histopathologic assessment*

Nuclear grade was classified according to the General Rules for Clinical and Pathological Recording of Breast Cancer 2005.[11] We assessed ER and PgR using mouse monoclonal antibody (Dako, Glostrup, Denmark). We defined receptor status using the Allred score, with a total score of 3 or more considered positive.[12] The HER2 score was analyzed by immunohistochemistry using the Hercep Test (Dako, Glostrup, Denmark).

*Statistical analysis*

We used t-test to compare the mean ADC values of Stage pT1 ($\leq$2 cm) versus pT2 or 3 (>2 cm) cancers, cancers with versus those without vascular invasion, N-positive versus N-negative cancers, ER-positive versus ER-negative cancers, and PgR-positive versus PgR-negative cancers. We analyzed correlations between the ADC value with NG and the HER2 score by rank test using Spearman's correlation coefficient. We did not analyze age statistically because all patients but one were at least 35 years old. For multivariate analysis, we used multiple linear regression to assess factors that showed significant differences in the univariate analysis. $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using Statcel (OMS, Tokorozawa, Japan).

## Results

Univariate analysis demonstrated significantly higher mean ADC value for N-positive (0.97 ± 0.20

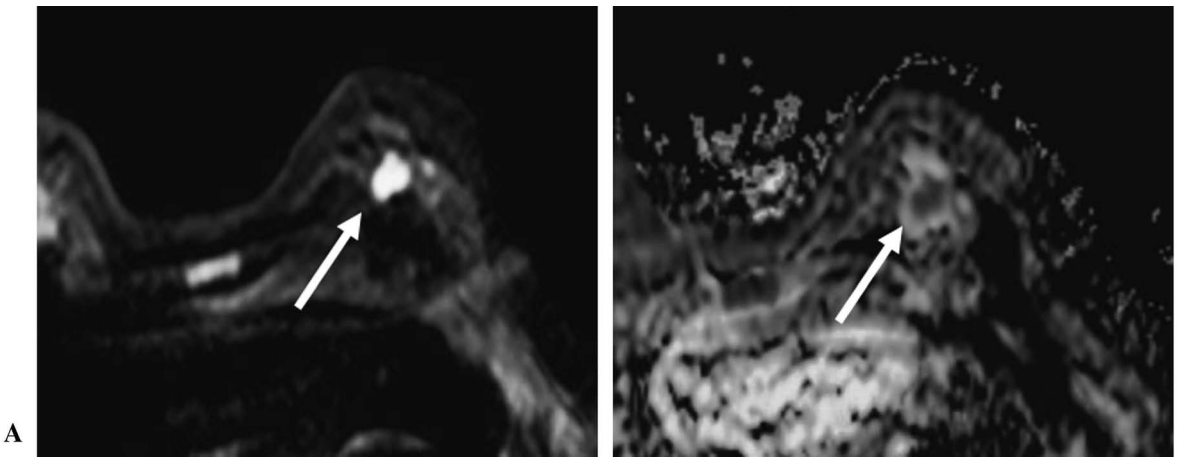


**Fig. 1.** A 46-year-old woman with left breast cancer diagnosed as axillary lymph node (N)-negative, nuclear grade (NG) 2, estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, and human epidermal growth factor receptor 2 (HER2) score 0. (**A**) A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI) (arrow). (**B**) The apparent diffusion coefficient (ADC) value was found to be $0.73 \times 10^{-3}$ mm$^2$/s on the ADC map.

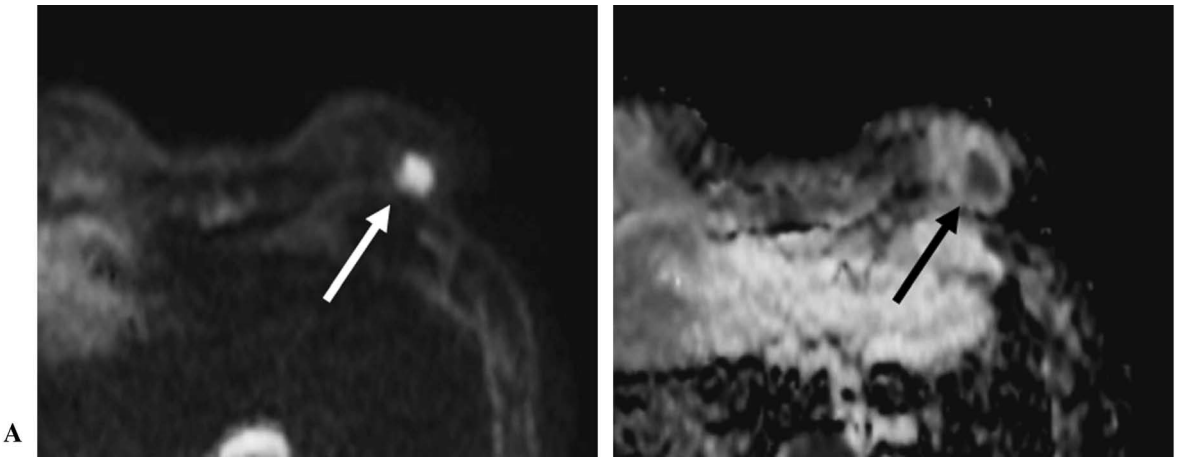


**Fig. 2.** A 56-year-old woman with left breast cancer diagnosed as axillary lymph node (N)-positive, nuclear grade (NG) 3, estrogen receptor (ER)-negative, progesterone receptor (PgR)-negative, and human epidermal growth factor receptor 2 (HER2) score 3+. (**A**) A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI). (**B**) The apparent diffusion coefficient (ADC) value was $1.10 \times 10^{-3}$ mm$^2$/s on the ADC map.

$\times 10^{-3}$ mm$^2$/s; n = 28) than N-negative cancers ($0.87 \pm 0.17 \times 10^{-3}$ mm$^2$/s; n = 53) ($P = 0.017$) (Fig. 4); significantly lower mean ADC value for ER-positive ($0.88 \pm 0.15 \times 10^{-3}$ mm$^2$/s; n = 63) than ER-negative cancers ($1.01 \pm 0.21 \times 10^{-3}$ mm$^2$/s; n = 18) ($P = 0.005$) (Fig. 5); and significantly lower ADC values for PgR-positive ($0.88 \pm 0.16 \times 10^{-3}$ mm$^2$/s; n = 47) than PgR-negative cancers ($0.95 \pm 0.18 \times 10^{-3}$ mm$^2$/s; n = 34) ($P = 0.048$) (Fig. 6). Mean ADC values did not differ significantly between Stage pT1 ($0.90 \pm 0.15 \times 10^{-3}$ mm$^2$/s; n = 58) and pT2 or pT3 breast cancers ($0.93 \pm 0.21 \times 10^{-3}$ mm$^2$/s; n = 23) ($P = 0.52$). Neither did ADC values differ significantly between breast cancers with ($0.92 \pm 0.18 \times 10^{-3}$ mm$^2$/s; n = 28) and without vascular invasion ($0.90 \pm 0.17 \times 10^{-3}$ mm$^2$/s; n = 53) ($P = 0.73$). The mean ADC value of cancers with NG1 was $0.89 \pm 0.16 \times 10^{-3}$ mm$^2$/s (n = 36); of NG2, $0.88 \pm 0.15 \times 10^{-3}$ mm$^2$/s (n = 18); and of NG3, $0.94 \pm 0.16 \times 10^{-3}$ mm$^2$/s (n = 27). There were no significant differences among them. The mean ADC values were $0.91 \pm 0.19 \times 10^{-3}$ mm$^2$/s for cancers with HER2 scores of 0 (n = 32); $0.92 \pm 0.11 \times 10^{-3}$ mm$^2$/s for those with score 1+ (n = 18); $0.93 \pm 0.22 \times 10^{-3}$ mm$^2$/s for those with score of 2+ (n = 17), and $0.86 \pm 0.13 \times 10^{-3}$ mm$^2$/s for those

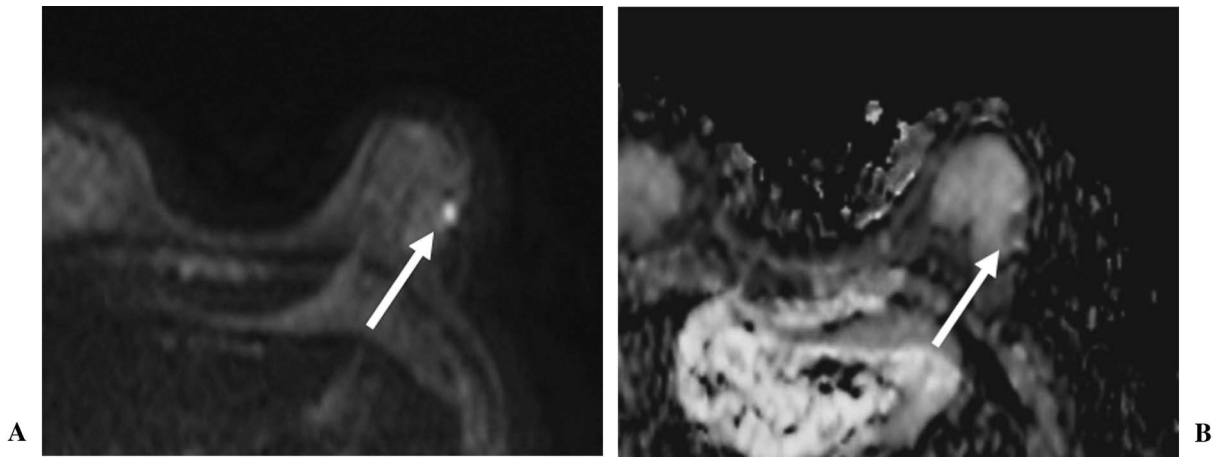


**Fig. 3.** A 49-year-old woman with left breast cancer diagnosed as axillary lymph node (N)-positive, nuclear grade (NG) 1, estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, and human epidermal growth factor receptor 2 (HER2) score 0. (**A**) A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI) (arrow). (**B**) The apparent diffusion coefficient (ADC) value was $1.24 \times 10^{-3}$ mm$^2$/s on the ADC map.

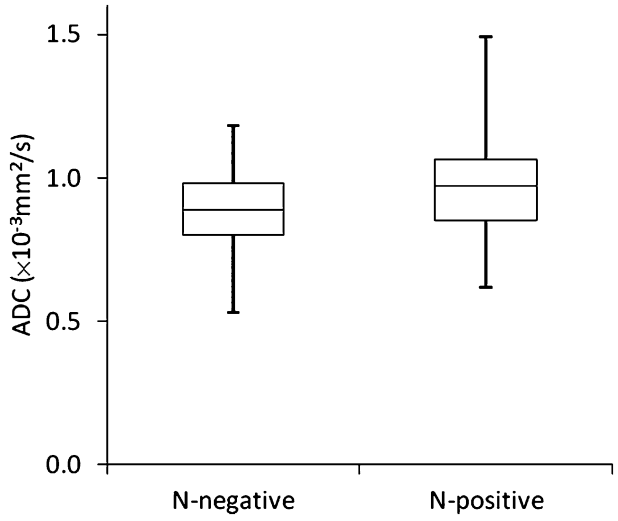


**Fig. 4.** Comparison of apparent diffusion coefficient (ADC) values between axillary lymph node (N)-negative and N-positive cancers. The mean ADC value of the N-positive cancers was significantly higher than that of the N-negative cancers ($0.97 \pm 0.20 \times 10^{-3}$ mm$^2$/s vs. $0.87 \pm 0.17 \times 10^{-3}$ mm$^2$/s) ($P = 0.017$).

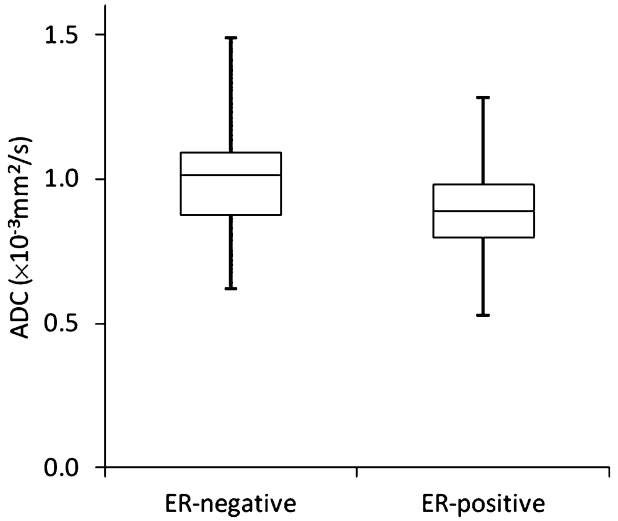


**Fig. 5.** Comparison of apparent diffusion coefficient (ADC) values between estrogen receptor (ER)-negative and ER-positive cancers. The mean ADC value of the ER-positive cancers was significantly lower than that of the ER-negative cancers ($0.88 \pm 0.15 \times 10^{-3}$ mm$^2$/s vs. $1.01 \pm 0.21 \times 10^{-3}$ mm$^2$/s) ($P = 0.005$).

with score of 3+ (n = 14). The HER2 score also showed no significant correlation with ADC. In the multivariate analysis, only N and ER were significant (Table).

## Discussion

The inverse correlation of tumor ADC values with tumor cellularity has been reported.[6,7] In this study, we observed higher ADC values for N-positive than N-negative cancers, and we speculate that the high ADC values in N-positive cancers may be attributable to a relatively large number of micronecroses or fibroses. The presence of fibrotic focus or necrosis is an important clinicopathological parameter associated with a higher degree of malignancy in IDCs.[13–16] One study reported significant association between the presence of nodal metasta-

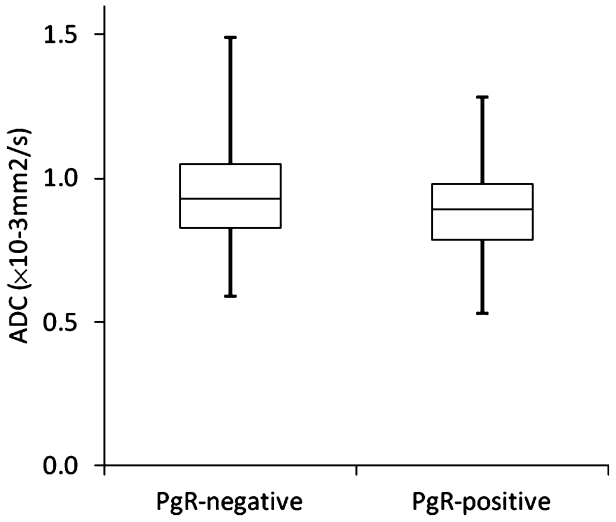


**Fig. 6.** Comparison of apparent diffusion coefficient (ADC) values between progesterone receptor (PgR)-negative and PgR-positive cancers. The mean ADC value of the PgR-positive cancers was significantly lower than that of the PgR-negative cancers ($0.88 \pm 0.16 \times 10^{-3}$ mm$^2$/s vs. $0.95 \pm 0.18 \times 10^{-3}$ mm$^2$/s) ($P = 0.048$).

**Table.** Multivariate analysis by multiple linear regression analysis

| Status | Regression coefficient | *P* value | 95% confidence interval |
|---|---|---|---|
| Axillary node | 0.11 | 0.005 | 0.03 ~ 0.18 |
| Estrogen receptor | −0.12 | 0.026 | −0.23 ~ −0.01 |
| Progesterone receptor | −0.01 | 0.83 | −0.10 ~ 0.08 |

sis and the presence of fibrotic focus.[17] King and associates contended that ADC value increased as the amount of necrosis increased and that areas of micronecrosis also contribute to the ADC value.[18] These findings support our results. Though we avoided apparent necrotic or cystic components, micronecrosis that was visually imperceptible by other sequences may have affected the ADC.

However, Kim and colleagues reported no correlation between ADC value and the presence of lymph node metastasis.[19] One reason our results differ may be because they included special type breast cancers other than IDC, but we excluded such special types. For example, mucinous carcinomas show higher ADC values than IDC,[7,20] but lymph node metastasis of mucinous carcinoma of the breast is rare.[21] Differences in tumor size might also affect the results, but Kim's group did not detail tumor size. We excluded patients with DCIS or IDC with invasive foci smaller than one cm because we thought the signal intensity of small lesions was unreliable on the ADC maps with the low resolution. In addition, the larger size of our study population than Kim's might account for the significant difference between our study findings.

In contrast, Razek and colleagues reported the opposite result.[22] They associated lower ADC values with the presence of axillary lymph nodes metastasis. These disparate results may be explained by the difference in study populations because larger tumor size is a risk factor for lymph node metastasis. Their study included many large (>5 cm) cancers, whereas the number of large cancers in our study was small because we excluded patients who had received neoadjuvant chemotherapy or endocrine therapy.

We observed lower ADC values for ER-positive than ER-negative cancers. Other authors reporting the same result[19,23–25] have inferred that ER inhibited the angiogenic pathway and induced a decrease in perfusion, thus affecting the ADC value. In addition, ER-positive tumors have shown high cellularity.[26–28] These results also support our finding of lower ADC values of ER-positive cancers. Despite a significant difference in the univariate analysis, PgR positivity and negativity showed no significant difference in the multivariate analysis. ER appears to have been the confounding factor that influenced PgR in the univariate analysis because it is known that most ER-positive cancers are also PgR-positive, and this applied to our series.

In this study, we did not analyze the prognosis itself, but prognostic factors. Further study evaluating recurrence or survival rate by long-term follow-up is required to clarify prognoses.

Our study has several limitations. Because SLNB has been reported to yield some false negatives,[29–31] some of our patients with lymph node metastasis may have been judged negative for metastasis based on their assessment by SLNB alone. Secondly, we did not include fluorescence *in situ* hybridization (FISH) analysis in this study for HER2 evaluation because it was not performed in some patients in the early period. According to recent guidelines, FISH analysis should be performed when the score is 2+ at immunohistochemistry. However, we believe this did not likely significantly influence our results because there were only minor differences among ADCs of 0, 1+, and 3+.

## Conclusion

ADC values were significantly higher for N-positive than N-negative breast cancers and significantly lower for ER-positive than ER-negative breast cancers.

## References


1. Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16:1569–1583.
2. Mussurakis S, Buckley DL, Horsman A. Prediction of axillary lymph node status in invasive breast cancer with dynamic contrast-enhanced MR imaging. Radiology 1997; 203:317–321.
3. Mussurakis S, Buckley DL, Horsman A. Dynamic MR imaging of invasive breast cancer: correlation with tumour grade and other histological factors. Br J Radiol 1997; 70:446–451.
4. Kvistad KA, Rydland J, Smethurst HB, Lundgren S, Fjøsne HE, Haraldseth O. Axillary lymph node metastases in breast cancer: preoperative detection with dynamic contrast-enhanced MRI. Eur Radiol 2000; 10:1464–1471.
5. Makkat S, Luypaert R, Stadnik T, et al. Deconvolution-based dynamic contrast-enhanced MR imaging of breast tumors: correlation of tumor blood flow with human epidermal growth factor receptor 2 status and clinicopathologic findings—preliminary results. Radiology 2008; 249:471–482.
6. Woodhams R, Matsunaga K, Iwabuchi K, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. J Comput Assist Tomogr 2005; 29:644–649.
7. Hatakenaka M, Soeda H, Yabuuchi H, et al. Apparent diffusion coefficients of breast tumors: clinical application. Magn Reson Med Sci 2008; 7:23–29.
8. Guo Y, Cai YQ, Cai ZL, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002; 16:172–178.
9. Woodhams R, Matsunaga K, Kan S, et al. ADC mapping of benign and malignant breast tumors. Magn Reson Med Sci 2005; 4:35–42.
10. Yabuuchi H, Matsuo Y, Okafuji T, et al. Enhanced mass on contrast-enhanced breast MR imaging: lesion characterization using combination of dynamic contrast-enhanced and diffusion-weighted MR images. J Magn Reson Imaging 2008; 28:1157–1165.
11. Sakamoto G, Inaji H, Akiyama F, et al. Japanese Breast Cancer Society. General rules for clinical and pathological recording of breast cancer 2005. Breast Cancer 2005; 12 Suppl:S1-S27.
12. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010; 28:2784–2795.
13. Hasebe T, Tsuda H, Hirohashi S, et al. Fibrotic foci in invasive ductal carcinoma: an indicator of high tumor aggressiveness. Jpn J Cancer Res 1996; 87:385–394.
14. Hasebe T, Tsuda H, Hirohashi S, et al. Fibrotic focus in infiltrating ductal carcinoma of the breast: a significant histopathological prognostic parameter for predicting the long-term survival of the patients. Breast Cancer Res Treat 1998; 49:195–208.
15. Jimenez RE, Wallis T, Visscher DW. Centrally necrotizing carcinomas of the breast: a distinct histologic subtype with aggressive clinical behavior. Am J Surg Pathol 2001; 25:331–337.
16. Colpaert C, Vermeulen P, Jeuris W, et al. Early distant relapse in ''node-negative'' breast cancer patients is not predicted by occult axillary lymph node metastases, but by the features of the primary tumour. J Pathol 2001; 193:442–449.
17. Hasebe T, Sasaki S, Imoto S, Mukai K, Yokose T, Ochiai A. Prognostic significance of fibrotic focus in invasive ductal carcinoma of the breast: a prospective observational study. Mod Pathol 2002; 15:502–516.
18. King AD, Ahuja AT, Yeung DK, et al. Malignant cervical lymphadenopathy: diagnostic accuracy of diffusion-weighted MR imaging. Radiology 2007; 245:806–813.
19. Kim SH, Cha ES, Kim HS, et al. Diffusion-weighted imaging of breast cancer: correlation of the apparent diffusion coefficient value with prognostic factors. J Magn Reson Imaging 2009; 30:615–620.
20. Woodhams R, Kakita S, Hata H, et al. Diffusion-weighted imaging of mucinous carcinoma of the breast: evaluation of apparent diffusion coefficient and signal intensity in correlation with histologic findings. AJR Am J Roentgenol 2009; 193:260–266.
21. Anan K, Mitsuyama S, Tamae K, et al. Pathological features of mucinous carcinoma of the breast are favourable for breast-conserving therapy. Eur J Surg Oncol 2001; 27:459–463.
22. Razek AA, Gaballa G, Denewer A, Nada N. Invasive ductal carcinoma: correlation of apparent diffusion coefficient value with pathological prognostic factors. NMR Biomed 2010; 23:619–623.
23. Jeh SK, Kim SH, Kim HS, et al. Correlation of the apparent diffusion coefficient value and dynamic magnetic resonance imaging findings with prognostic factors in invasive ductal carcinoma. J Magn Reson Imaging 2011; 33:102–109.
24. Martincich L, Deantoni V, Bertotto I, et al. Corre-

lations between diffusion-weighted imaging and breast cancer biomarkers. Eur Radiol 2012; 22: 1519–1528.
25. Choi SY, Chang YW, Park HJ, Kim HJ, Hong SS, Seo DY. Correlation of the apparent diffusion coefficiency values on diffusion-weighted imaging with prognostic factors for breast cancer. Br J Radiol 2012; 85(1016):e474–479.
26. Antoniades K, Spector H. Correlation of estrogen receptor levels with histology and cystomorphology in human mammary cancer. Am J Clin Pathol 1979; 71:497–503.
27. Hawkins RA, Roberts MM, Forrest AP. Oestrogen receptors and breast cancer: current status. Br J Surg 1980; 67:153–169.
28. Black R, Prescott R, Bers K, Hawkins A, Stewart H, Forrest P. Tumour cellularity, oestrogen receptors and prognosis in breast cancer. Clin Oncol 1983; 9:311–318.
29. Bonnema J, van de Velde CJ. Sentinel lymph node biopsy in breast cancer. Ann Oncol 2002; 13:1531–1537.
30. Zavagno G, Del Bianco P, Koussis H, et al. Clinical impact of false-negative sentinel lymph nodes in breast cancer. Eur J Surg Oncol 2008; 34:620–625.
31. Collins CD. The sentinel node in breast cancer: an update. Cancer Imaging 2005; 5 Spec No A:S3-S9.