Original Article

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Whole-Body Magnetic Resonance Imaging is Associated with Survival Time in Metastatic Breast Cancer

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Abstract

Background: Few studies have assessed the association between prognosis and apparent diffusion coefficient (ADC) or tumor volume in metastases from breast cancer.

Purpose: To evaluate whether tumor volume and ADC on postoperative whole-body magnetic resonance imaging (WB-MRI), including WB diffusion-weighted imaging (WB-DWI), in the follow-up period are predictors of prognosis in patients with metastatic breast cancer.

Methods: 87 patients who underwent WB-MRI in the post-operative follow-up period between October 2015 and March 2020 were enrolled in this retrospective study. Metastatic tumors initially depicted on WB-DWI were segmented semi-automatically. The correlation between tumor diffusion volume (tDV) and minimum ADC extracted from WB-DWI and survival time was investigated. Receiver-operating characteristic analysis was performed and the area under the curve (AUC) was calculated. The optimal cut-off value to predict survival was obtained and sensitivity and specificity were calculated. Survival rate was compared between groups above and below the cut-off value.

Results: During the study, one patient died of a myocardial infarction, leaving a final total of 86 patients. Of the 86 patients, 38 died. Cox proportional hazard modeling showed that tDV and minimum ADC were prognostic factors. The AUC for tDV was 0.720. A cut-off value of 24.3 mL respectively. Patients with tDV>24.3 mL showed a significantly lower survival rate ($p<0.0001$). The AUC for minimum ADC was 0.710. A cut-off value of 0.084×10^{-3} mm^2/s respectively. Patients with min ADC$<0.084 \times 10^{-3}$ mm^2/s showed a significantly lower survival rate ($p<0.0001$).

Conclusion: Postoperative follow-up with WB-MRI could predict medium-term prognosis in patients with distant metastases of breast cancer.

Key words: Breast cancer, distant metastasis, whole-body MR imaging, diffusion-weighted imaging

Introduction

Breast cancer is the most prevalent cancer and the leading cause of cancer death among women worldwide[1)]. Approximately half of women diagnosed with breast cancer develop metastatic disease and distant metastasis remains the underlying cause of death in the majority of breast cancer patients. Following a diagnosis of metastatic disease, the average survival time is 18−30 months[2)]. Breast cancer metastases are found mainly in bone, lungs and liver.

Prognostic factors for primary breast cancer have been known. Tumor size and nodal involvement have been regarded as independent prognostic factors

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that are incorporated into TNM stages. Others include histological findings; histological tumor grade, hormone status and Ki-67 index[3,4]. Hormone status is related to molecular subtypes. Regarding imaging study, a recent study suggested that the apparent diffusion coefficient (ADC) of the primary tumor might serve as a prognostic factor for breast cancer[5, 6]. However, the prognostic factors for metastatic breast cancer have not been established although one study investigated the factor for the patients with brain metastasis[7]. Whether the factors for the primary breast tumor is applied to predict the prognosis of the patients with metastasis is uncertain. The histopathological findings may be applicable similar to primary breast cancer; however, in the clinical practice the metastasis has been usually diagnosed clinically but not pathologically. A previous study revealed that the volume of bone metastasis was associated with overall survival (OS) by quantifying bone metastasis using whole-body diffusion-weighted imaging (WB-DWI) in metastatic castration-resistant prostate cancer[8]. If imaging biomarkers for the metastatic lesions of breast cancer were available, it would be beneficial due to non-invasiveness.

WB-DWI has emerged as a useful assessment tool for the detection and therapeutic monitoring of bone metastases[9, 10]. Commercially available software can now measure the tumor volume and ADC of multiple metastatic lesions that have been segmented from WB-DWI[11].

The purpose of this study was thus to investigate whether tumor volume and ADC of whole-body magnetic resonance imaging (WB-MRI), including WB-DWI, can predict prognosis in patients with metastatic breast cancer.

Materials and methods

Patient Population

Patients comprised 775 women who underwent WB-MRI including WB-DWI in the post-operative follow-up period for breast cancer between October 2015 and March 2020. We excluded the patients without distant metastasis, those with unknown pathological diagnosis, and those who had undergone first-line treatment for distant metastasis prior to WB-MRI. The final collection of clinical data was on December 13, 2024. Patients alive at the time of the final data collection were classified as surviving patients, while those censored during the follow-up period were also considered survivors. This study was approved by our institutional review board of St. Marianna University School of Medicine (approval No. 3889), and the requirement for informed consent was waived due to the retrospective nature of the study.

MRI technique

WB-MRI was performed using a 1.5-T MRI scanner (Achieva; Philips Healthcare, Best, the Netherlands) with a 16-channel surface/body radiofrequency coil, with the patient in the supine position. Axial images were acquired with free breathing. The scan parameters are listed in **Table 1**. The total acquisition time was 26 minutes.

Image analysis

The initial WB-DWI (b value=1000 s/mm^2) examinations were retrospectively analyzed for metastatic disease in organs using commercially available software (BD-Score version 1.2; PixSpace, Fukuoka, Japan). Two radiologists (Reader 1 with 19 years of experience, Reader 2 with 21 years of experience in breast imaging) assessed hyperintense lesions on WB-DWI with reference to the T1- and T2-weighted images (**Figure 1a, b, c**), and the presence of metastatic lesions was determined by consensus. Any images obtained by other modalities were also available for reference.

Hyperintense lesions detected in the organs on WB-DWI were initially segmented semi-automatically. Some organs, such as normal spleen and intestinal tract, were also segmented and deleted manually. Lesions that were missed by semi-automatic segmentation were manually encircled using a region of interest or segmented by the region-growing method and were finally segmented by colored mask (**Figure 1d, e**). Reader 1 conducted the segmentation of lesions twice at an interval of 4 months, and Reader 2 performed segmentation once. Four kinds of ADC values were automatically calculated and recorded for all segmented lesions in each patient, which comprised of minimum, 25th percentile, mean, and median ADCs. Tumor volume, here defined as tumor diffusion volume (tDV), was also automatically measured and recorded simultaneously. Brain metastases were excluded from analysis because part of the brain was outside the scanning area.

Pathological evaluation

Pathological diagnoses were retrieved from the electronic medical records of each patient. All tissue specimens were examined by a pathologist with more than 11 years of experience in breast pathology. All

Table 1. Scan Parameters for Whole-Body MRI

Plane	Sequence	FOV (mm)	Matrix	Coverage (mm) / slice (mm)	Resolution (mm)	TR/TE (ms)	Scan time	Other
Transverse	DWI	450*450	92*91	240 / 5	4.9*4.9*5.0	6645 / 71	3 min 32 s	b:1000 TSE f:31
	STIR	450*450	208*207	240 / 5	2.1*2.1*5.0	4203 / 80	50 s	TSE f:54
	T1WI	450*450	224*217	240 / 5	2.0*2.0*5.0	591 / 19	39 s	TSE f:8
Coronal	T2WI	240*446	132*242	196 / 7	1.8*1.8*7.0	9064 / 70	9 s	TSE f:88
	T1WI	240*446	132*240	196 / 7	1.8*1.8*7.0	597 / 17	31 s	TSE f:7
Sagittal	T1WI	240*240	148*147	100 / 4	1.6*1.6*4.0	497 / 16	24 s	TSE f:7

DWI, diffusion-weighted imaging; STIR, short inversion-time inversion recovery; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; FOV, field of view; TR, repetition time; TE, echo time; TSE f, turbo spin-echo factor.
b: b-value, s/mm^2

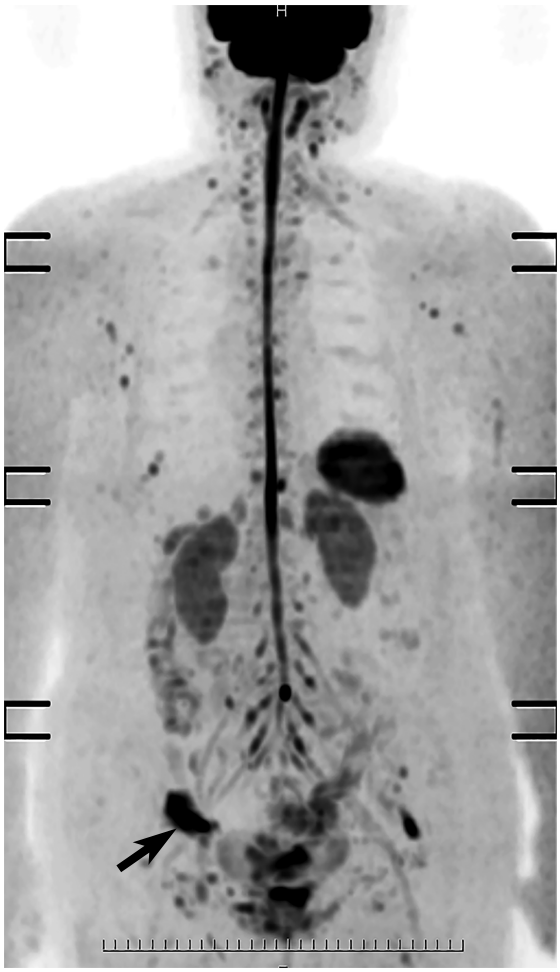
patients underwent core-needle breast biopsy or vacuum-assisted biopsy (depending on the location of the lesion) by mammogram or with ultrasonographic guidance. Final pathological diagnoses were made based on examination of surgical specimens. The intrinsic lesion subtype was determined based on the presence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). ER and PgR were considered positive if>10% of nuclei stained positively. HER2 was evaluated using the Hercep Test (Dako, Glostrup, Denmark) and scored on a scale from 0 to 3+. Tumors with a score of 3+, or with a score of 2+and a ≥ 2.2-fold increase in HER2 gene amplification (as determined by fluorescence in situ hybridization) were considered positive for HER2 overexpression. In addition, Ki-67 index, an indicator of cancer cell proliferative capacity, was also recorded.

Statistical analysis

First, the Shapiro-Wilk test was used to examine whether the data were normally distributed.

Spearman's correlation was performed to evaluate the relationship between tDV and survival time.

a



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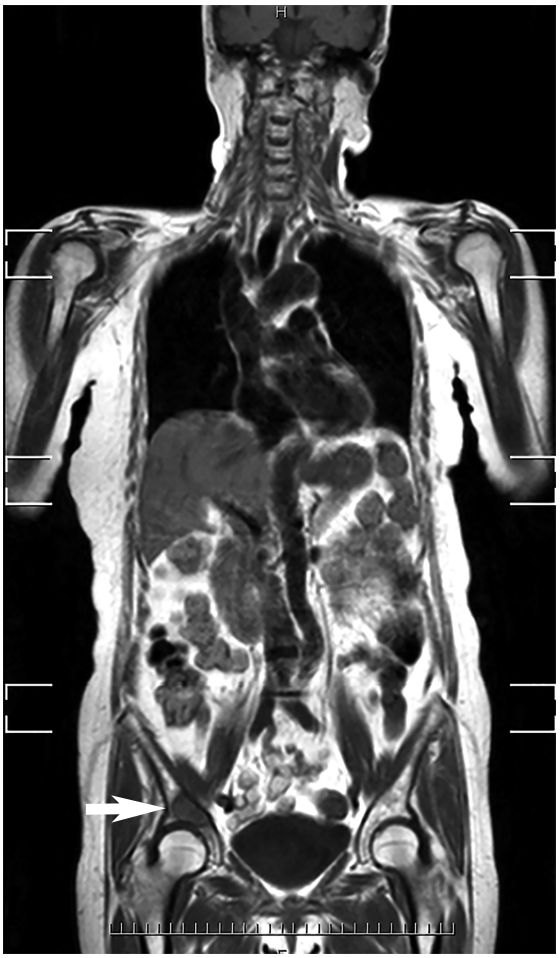

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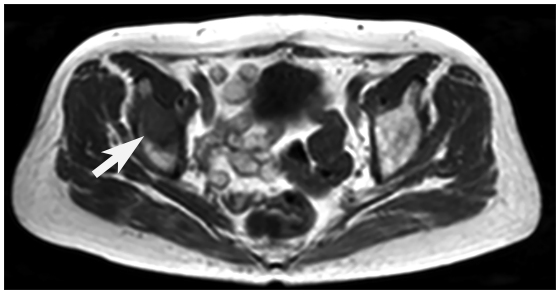

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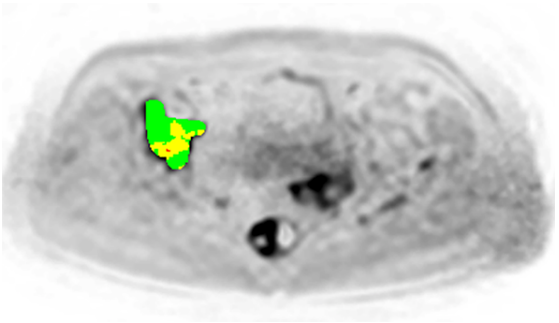

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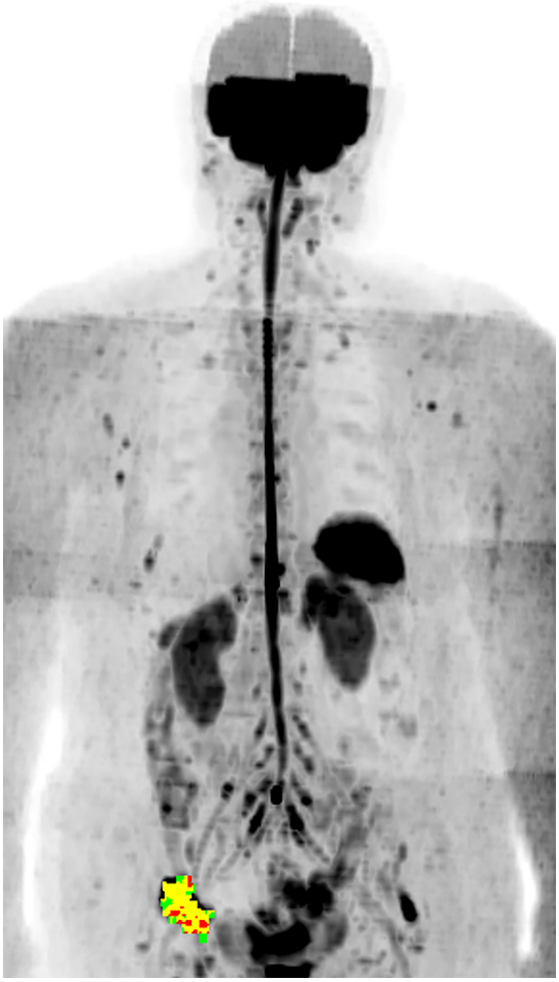

Figure 1. A 72-year-old woman with bone metastasis

a) Maximum intensity projection (MIP) image of whole-body diffusion-weighted imaging (WB-DWI) in the coronal plane shows a hyperintense lesion in the right ilium (arrow).

b) T1-weighted coronal image demonstrates the hypointense lesion in the right ilium, which correlates to that of Figure 2a (arrow). The iliac lesion was diagnosed with bone metastasis.

c) T1-weighted axial image also demonstrates the identical lesion in the right ilium (arrow).

d) The hyperintense lesion on the axial DWI was encircled by a colored mask semi-automatically. The mask was modified by radiologist 1, if necessary.

e) MIP image generated by the software (different to image 2a) demonstrates the overlaid colored mask that was set on the axial images for measurements. The tumor diffusion volume is 23.4 mL. Minimum apparent diffusion coefficients is 0.308×10^{-3} mm^2/s.

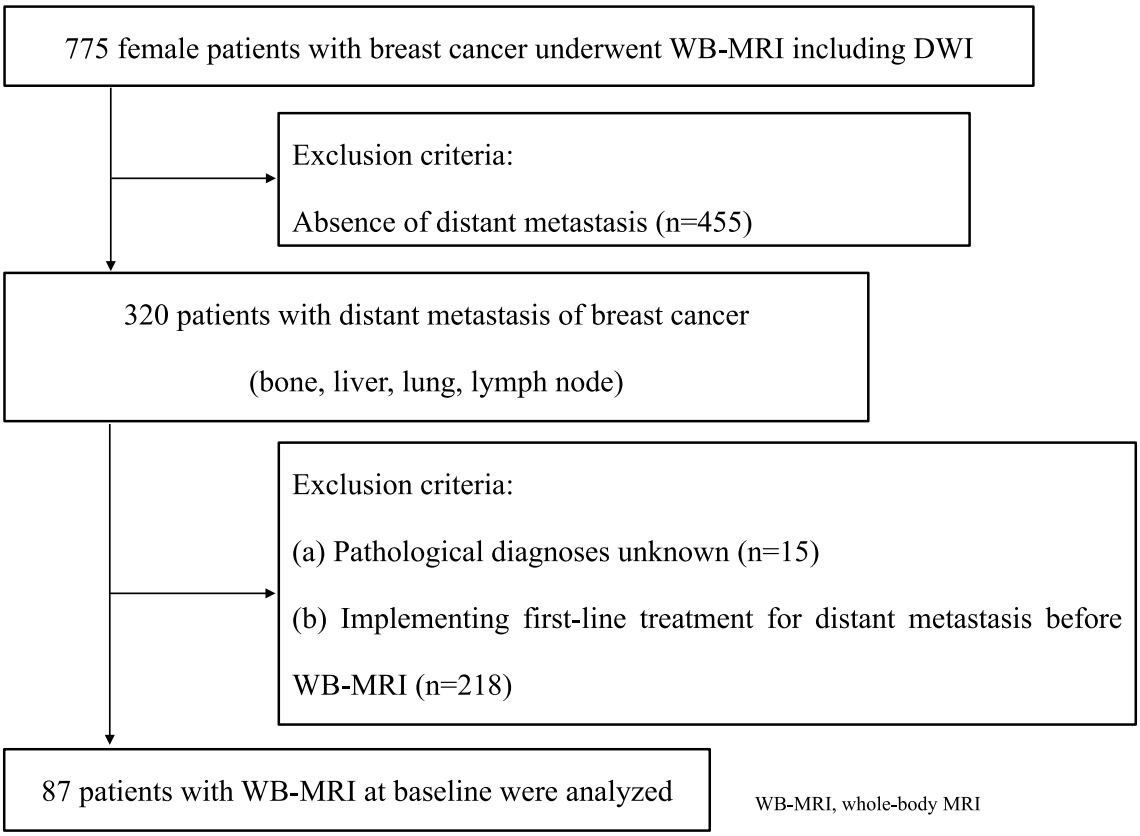

Figure 2. Flowchart of the study selection process

Cox proportional hazard modeling was employed to identify factors significantly associated with survival time. With the number of deaths increasing up to 38, four variables were tested in the Cox proportional hazard model. Hormone status and Ki-67 index, both commonly recognized as prognostic factors for primary breast cancer[3, 4], were included as variables in the analysis. To characterize the ability of significant factors to predict prognosis, receiver-operating characteristic (ROC) analysis was performed and the area under the curve (AUC) was calculated. The cut-off value to discriminate between survivors and deceased patients was determined using the Youden index, and sensitivity and specificity were then obtained based on this index. Survival rate was compared between the groups with more than the cut-off value and others using Kaplan—Meier analysis and the log-rank test. The intraclass correlation coefficient (ICC) was used to determine interobserver and intraobserver reliability of tDV and ADCs. JMP Pro version 14.2 software (SAS Institute, Cary, NC, USA) was used to process the data and conduct statistical analyses. In all analyses, values of $p<0.05$ were taken to indicate statistical significance.

Results

Patient population

We excluded 455 patients who had no distant metastasis, 15 patients for whom the pathological diagnosis was unknown, and 218 patients who had undergone first-line treatment for distant metastasis prior to WB-MRI. A final total of 87 patients were thus enrolled in the study (**Figure 2**). However, during the course of the study, one person died of myocardial infarction, so the final total of 86 patients were enrolled. The ages ranged from 28 to 88 years old (median, 54.5 years). Twenty-three patients in whom distant metastasis had been detected by other modalities underwent WB-MRI early in the study period, and all other patients underwent WB-MRI with no known distant metastases. Other imaging modalities included bone scintigraphy, ultrasound, computed tomography (CT), MRI, and positron emission tomography (PET) -CT.

Table 2. Histological Types and Subtypes of Breast Cancer

Histological type (n=86)	
Invasive ductal carcinoma	78
Invasive lobular carcinoma	6
Mucinous carcinoma	1
Squamous cell carcinoma	1
Subtype (n=86)	
Luminal A	35
Luminal B	36
HER2	6
Triple-negative	7
Unknown	2

Thirty-eight of the 86 patients (44.2%) died during follow-up. The survival time from the first WB-MRI ranged from 18 to 2551 days (median, 764 days) in the deceased patients and from 160 to 3073 days (median, 1988 days) in the survival patients.

Pathological evaluation

In all patients, the pathological diagnosis of primary breast cancer was made by histological examination of the surgical specimen. The histological types are listed in **Table 2**. Invasive ductal carcinoma (IDC) was the most common type (90%), of which 82% were luminal A or B histological subtype (**Table 2**).

Image analysis

Images from the first WB-MRI examination that depicted distant metastases were included in the analysis. WB-MRI detected bone metastases in 47 patients, liver metastases in 25 patients, lung metastases in 15 patients, and lymph node metastases in 28 patients. Metastatic lesions detected by WB-MRI correlated with those detected by other modalities. The median of the number of metastatic lesions per patient that were detected first by WB-MRI was 2.5 (range, 1−48) for bone, 3 (range, 1−58) for liver, 3 (range, 1−11) for lungs, and 1 (range, 1−13) for lymph nodes.

Association of prognostic factors with survival

tDV showed a negative correlation with survival time ($r=-0.40$, $p<0.001$). Cox proportional hazard model analysis was conducted for tDV and minimum ADC revealed that tDV (hazard ratio,1.003; 95% confidence interval, 1.002−1.005; $p<0.0001$) and minimum ADC (hazard ratio, 0.082; 95% confidence interval, 0.009−0.746; $p=0.0264$) were independent prognostic predictors.

ROC analysis of tDV and minimum ADC was performed to obtain the AUC and to determine the cut-off value for predicting survival. The AUC values for tDV and minimum ADC were 0.720 and 0.710, respectively, with the cut-off values at maximum Youden index for predicting survival determined to

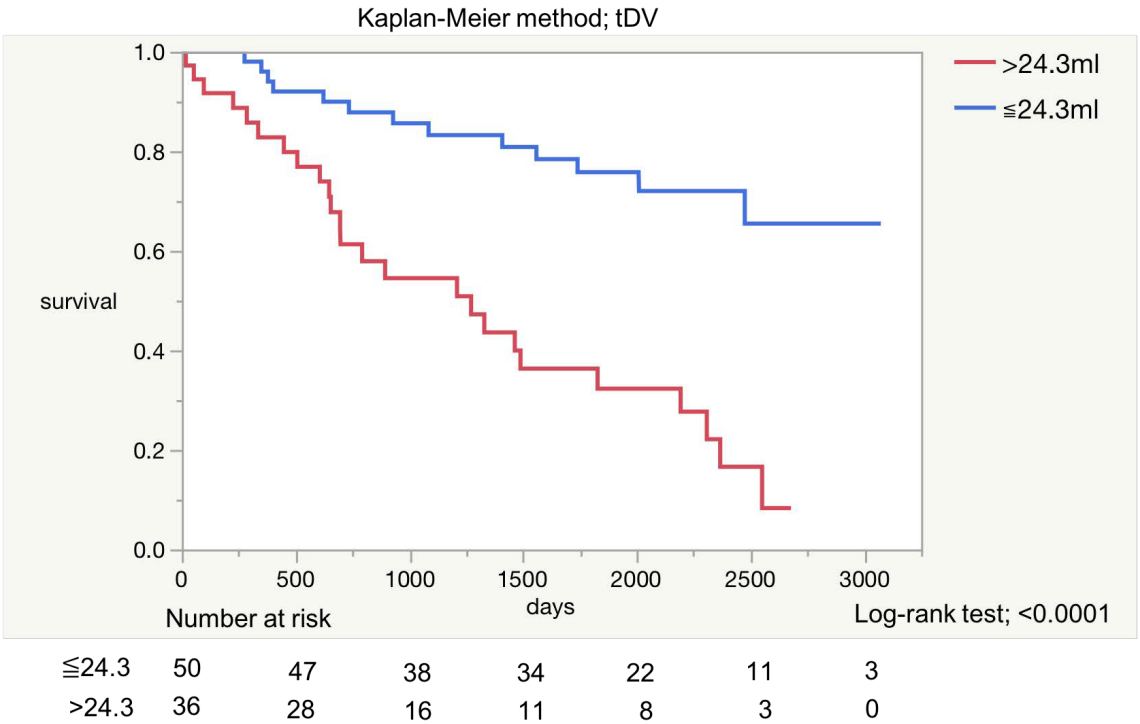

Figure 3. Kaplan—Meier method and log-rank test; tDV
Kaplan—Meier plots at tDV cut-off value of 24.3 mL. (Log-rank test; P<0.0001).

be 24.3 mL for tDV and 0.084×10^{-3} mm^2/s for minimum ADC.

Kaplan—Meier method and log-rank test

Survival rate was significantly lower in patients with tDV>24.3 mL than in those with tDV≦24.3 mL (Log-rank test; p<0.0001, **Figure 3**). Similarly, survival rate was significantly lower in patients with minimum ADC<0.084×10^{-3} mm^2/s compared to those with minimum ADC≧0.0084×10^{-3} mm^2/s (Log-rank test; p<0.0001, **Figure 4**).

Intraobserver and interobserver reliability

ICCs for intraobserver (Reader 1) comparison were 0.9987 and 0.696 for tDV and minimum ADC, respectively. ICCs for interobserver comparison were 0.9994 and 0.646 for tDV and minimum ADC, respectively.

Discussion

Our study demonstrated that tDV and minimum ADC of all tumors in patients with distant metastases from breast cancer before commencing chemotherapy were independent prognostic factors. These findings suggest that in addition to its ability to detect metastases, WB-MRI could provide an efficient method for predicting prognosis.

The heterogeneous histological characteristics of malignant tumors could play an important role in the representation of malignant potential by ADCs. When tumors are densely packed with malignant cells, the resulting ADC histogram may be less skewed and spread out, so differences in the evaluated ADC parameters may be less pronounced. Conversely, mean or median ADCs may be higher if the lesions are heterogeneous in cellularity, and lower percentile ADCs may be more accurate for assessing malignant potential. A previous study found that 10th percentile ADCs outperformed mean and median ADCs in differentiating low-grade tumors from intermediate- or high-grade prostate cancers[12]. Distant metastasis of breast cancer involves multiple organs, such as bones, liver, lungs and lymph nodes, and is thus expected to be more heterogeneous than those of prostate cancer. In the present study, some metastases involved multiple organs and were heterogeneous due to variability of size and internal intensity. In addition, the whole tumor was segmented to measure tumor volume, leading to the inclusion of heterogeneous areas that contained necrotic components. We therefore specu-

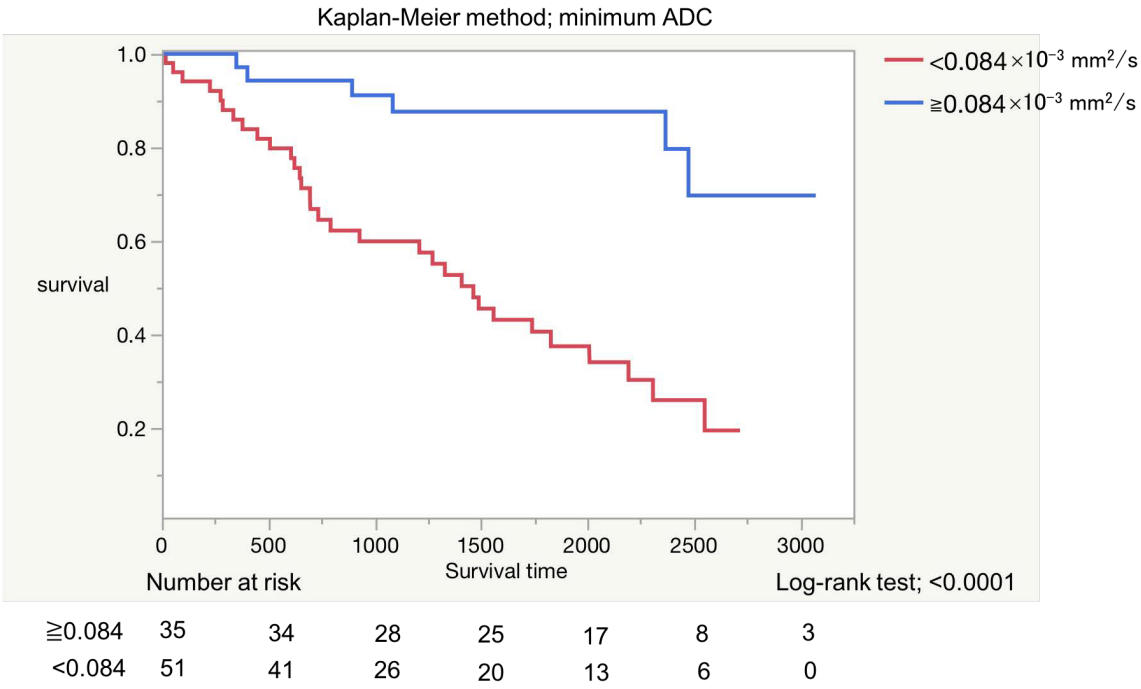

Figure 4. Kaplan—Meier method and log-rank test; minimum ADC
Kaplan—Meier plots at minimum ADC cut-off value of 0.084×10^{-3} mm^2/s. (Log-rank test; P<0.0001).

late that significant differences may have been present in the minimum ADC values among the multiple parameters in our results, and reproducible representation by ADC values could therefore be difficult.

tDV of all metastatic tumors of breast cancer was a significant indicator of survival time from the detection of metastases. In castration-resistant prostate cancer, the tDV of bone metastases correlated significantly with OS[8], and prognosis worsened as tDV increased. Although diameter of the primary tumor has been reported as a prognostic indicator in breast cancer[3, 4, 13, 14], one study has demonstrated that the volume of brain metastatic tumors derived from DWI correlates with metastatic progression-free survival, but not with OS[7]. Compared with that of prostate cancer, distal metastasis of breast cancer often involves multiple organs and emerges at different times in different organs[15, 16]. Survival time derived on the basis of tumor volume thus differs from organ to organ even within the same patient, and survival time is biased according to the organ involved. For example, in the case of liver metastasis newly discovered in a patient with bone metastasis, liver metastasis could be a poorer prognostic factor than bone metastasis because survival time is shorter for liver metastasis. Because it is difficult to compare the predictive ability of each organ for survival time, a more practical solution is to examine the prognostic value of the total metastatic volume in all organs prior to the implementation of chemotherapy. In addition, the method for measuring tumor volume is simpler than that for measuring ADC. In fact, the intraobserver and interobserver reliability of tDV was higher than that of minimum ADC. Metastatic tumors may include a necrotic component; however, tumor volume is a significant predictor of survival time even without removing the necrotic component. Accordingly, the volume of all organs can be summed without the need for a representative value, as with ADC.

Subtype and Ki-67 index that were well known factors of primary breast cancer related to the prognosis were not associated with survival in this study. The prognostic factors of primary breast cancer would be predictable for the clinical course including the recurrence or metastasis. However, whether they can be applied to predict the prognosis of the patients once after metastasis occurs is uncertain. The prognostic factors for metastatic breast cancer have not been established. The pathological findings of metastatic lesions may be applicable similar to primary breast cancer; however, in the clinical practice the metastasis has been usually diagnosed clinically but

not pathologically. Therefore, we have focused on the imaging factors that could be biomarkers, ADCs and tDV, according to the previous study for castration-resistant prostatic cancer[8]. Further analysis incorporating additional subtypes and Ki-67 index, a well-known prognostic factor for primary breast cancer[3,4], revealed significant differences in minimum ADC and tDV, but not in subtypes or Ki-67 index.

WB-DWI has not been widely implemented for metastatic breast cancer because there is a lack of standardization. In contrast, METastasis Reporting and Data System for Prostate Cancer (MET-RADS-P) and Myeloma Response Assessment and Diagnosis System (MY-RADS) have been proposed to standardize the MR protocols and assessment of response in prostate cancer and multiple myeloma, respectively[17, 18]. These systems include the response assessment category for bone lesions and Response evaluation criteria in solid tumors (RECIST) v1.1 for other lesions such as soft tissue and lymph nodes, and may also be applied to breast cancer. However, as metastatic lesions in breast cancer frequently involve multiple organs, including the brain, we question their adequacy for breast cancer. At the very least, the scanning protocols should be standardized to minimize their influence on measurement of tumor volume and ADC value.

Some limitations of our study must be considered. Firstly, the number of patients was small. The tDV and ADC values obtained may have been also affected by the small number of subjects. Further studies in larger populations are needed. A larger population would provide different cut-off values that may provide higher AUC, sensitivity, and specificity. Secondly, as only one case of brain metastasis was seen in our study, we did not include brain metastases in this analysis. We consider that this exclusion did not negatively impact the results, although the brain is a common site of metastasis. Modification of our protocol to take brain metastases into consideration may be necessary. Thirdly, the time between date of surgery and first WB-MRI during follow-up was not constant, and some patients underwent WB-MRI after metastases had already been detected by other modalities. In such cases, survival time was biased. An exact protocol for implementing WB-MRI in the follow-up period is required. Fourthly, in this study we conducted an exploratory analysis and did not investigate a causal relationship.

Conclusion

tDV and minimum ADC of distant metastases from breast cancer in involved organs correlated significantly with medium-term survival time. Postoperative WB-MRI during follow-up is clinically practical because it can detect distant metastatic lesions and also predict prognosis through the calculation of tDV and measurement of minimum ADC.

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Author contributions

YK conceived and designed the study. YK and TY collected the data. YK and TY analyzed and interpreted the data. HM provided overall guidance throughout the research process. All authors contributed to the drafting and revision of the manuscript and approved the submitted version. All authors take responsibility for the accuracy and completeness of the work and are accountable for addressing any related questions regarding its integrity.

Conflicts of interest

The authors have nothing to disclose.