

Original Article

Received: August 3, 2021
Revised: October 8, 2021
Accepted: October 8, 2021

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of Magnetic Resonance in
Medicine (KSMRM)

Benefit of Using Early Contrast-Enhanced 2D T2-Weighted Fluid-Attenuated Inversion Recovery Image to Detect Leptomeningeal Metastasis in Lung-Cancer Staging

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Purpose: To evaluate the clinical benefit of 2D contrast-enhanced T2 fluid-attenuated inversion recovery (CE-T2 FLAIR) image for detecting leptomeningeal metastasis (LM) in the brain metastasis work-up for lung cancer.

Materials and Methods: From June 2017 to July 2019, we collected all consecutive patients with lung cancer who underwent brain magnetic resonance image (MRI), including contrast-enhanced 3D fast spin echo T1 black-blood image (CE-T1WI) and CE-T2 FLAIR; we recruited clinico-radiologically suspected LM cases. Two independent readers analyzed the images for LM in three sessions: CE-T1WI, CE-T2 FLAIR, and their combination.

Results: We recruited 526 patients with suspected lung cancer who underwent brain MRI; of these, we excluded 77 (insufficient image protocol, unclear pathology, different contrast media, poor image quality). Of the 449 patients, 34 were clinico-radiologically suspected to have LM; among them, 23 were diagnosed with true LM. The calculated detection performance of CE-T1WI, CE-T2 FLAIR, and combined analysis obtained from the 34 suspected LM were highest in the combined analysis (AUC: 0.80, 0.82, and 0.89, respectively). The inter-observer agreement was also the highest in the combined analysis (0.68, 0.72, and 0.86, respectively). In quantitative analyses, CNR of CE-T2 FLAIR was significantly higher than that of CE-T1WI (Wilcoxon signed rank test, $P < 0.05$).

Conclusion: Adding CE-T2 FLAIR might provide better detection for LM in the brain-metastasis screening for lung cancer.

Keywords: Meningeal carcinomatosis; Lung neoplasms; Magnetic resonance imaging; Contrast media; Diagnosis

INTRODUCTION

Leptomeningeal metastasis (LM) is an uncommon complication in patients with solid tumors and occurs in about 4–15% cases (1). Since LM has a poor prognosis, with deaths reported to occur within four to six weeks of detection because of neurologic dysfunction if untreated (2), the importance of early and accurate diagnosis cannot be overemphasized. Moreover, the clinical need for diagnosis and treatment-response monitoring of LM has increased further as the prognosis has gradually improved with the recent advent of drugs that improve central nervous system (CNS) penetration and the development of new treatment options, such as immunotherapy (3). Unfortunately, the diagnosis and monitoring of LM is challenging (4). For cerebrospinal fluid (CSF) cytology, the sensitivity is very low, at 50–60%, and there are risks and inconveniences involved, especially when repeated examinations are required (2).

In response to these clinical needs, there have been radiologic studies for LM diagnosis. Recent studies have shown that a contrast-enhanced 3D T1 black-blood fast spin-echo image (CE-T1WI) is better for LM detection than is a 2D spin-echo (SE) T1 weighted image (T1WI) or 3D gradient echo (GRE) T1WI (5). In contrast, some studies have shown that a contrast-enhanced (CE) fluid-attenuated inversion recovery image (FLAIR) is helpful in the diagnosis of leptomeningeal pathology, including meningitis or LM (6–8). However, since the incidence of LM is relatively low, CE-T2 FLAIR is not widely used in routine practice, because the clinical MR protocol setting requires an essential image within a limited time (9). However, recent developments of MR techniques, including parallel imaging or compressed sensing, allow less scan time without the degradation of image quality (10, 11) and so allow more time for additional sequences. Therefore, we aimed to evaluate the clinical benefit of 2D CE-T2 FLAIR for the detection of LM in the brain metastasis work-up for lung cancer.

MATERIALS AND METHODS

Study Design and Participants

This retrospective study was approved by our institutional review board, and written informed consent was waived. We recruited all consecutive 526 patients with lung cancer who underwent brain CE-MRI from June 2017 to July 2019. Of these, we excluded 77 patients for the following reasons: both CE-T1WI and CE-T2 FLAIR were not included

at the same image session ($n = 62$); unclear lung-cancer pathology ($n = 11$); different contrast media ($n = 3$); or poor image quality ($n = 1$). We considered 449 patients eligible for risk-factor analyses. For patients with two or more scans, we used the earliest MR scan that demonstrated LM, if LM was suspected. We used the initial image if it was negative during the study period. Among the patients, we recruited 34 who had suspected LM on radiologic reports by daily practice or clinically suspected LM and for whom CSF cytology was done for qualitative analyses. In addition, among the 34 participants, 23 were finally diagnosed to have true LM according to the National Comprehensive Cancer Network guidelines and previous literature (12–14) by our attending neuro-oncologist (C.K.K., 22 years of experience). The radiologic and clinical findings used in the final diagnosis are shown in Supplementary Table 1. Among the 23 confirmed participants, we excluded 3 because of visualization on only one sequence. Finally, we considered 20 patients to be eligible for quantitative analyses. Figure 1 summarizes the study design and the number of patients included in each analysis.

Imaging Acquisition

We obtained all MR images with 3-T scanners (Signa HDx, GE Healthcare, Milwaukee, WI, USA/MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) with dedicated head coils (8 channels for Signa HDx; 64 channels for MAGNETOM Skyra). We randomly assigned the patients according to our MRI room schedule. For both groups, after we injected 0.2 mL/kg gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France) as a bolus, we obtained CE-images in the order of CE-T2 FLAIR and CE-T1WI. We obtained the CE-T2 FLAIR images by axial plane in 5-mm thickness and CE-T1WI by sagittal T1WI with 1-mm section thickness, isovoxel. Detailed MR parameters for CE-T2 FLAIR and CE-T1WI of each MR machines are summarized in Supplementary Table 2.

Image Analysis

For qualitative analyses, we used the MR images of the 34 patients suspected for LM. A retrospective and blind review was done by a subspecialty-trained radiologist (J.B.L., 7 years of experience) and a third-year radiology resident. Image review consisted of three sessions: CE-T1WI only, CE-T2 FLAIR only, and combined CE-T1WI and CE-T2 FLAIR. For each session, we evaluated each patient for LM through visual interpretation. To minimize the recall bias, we randomly assigned the image order for each session, and

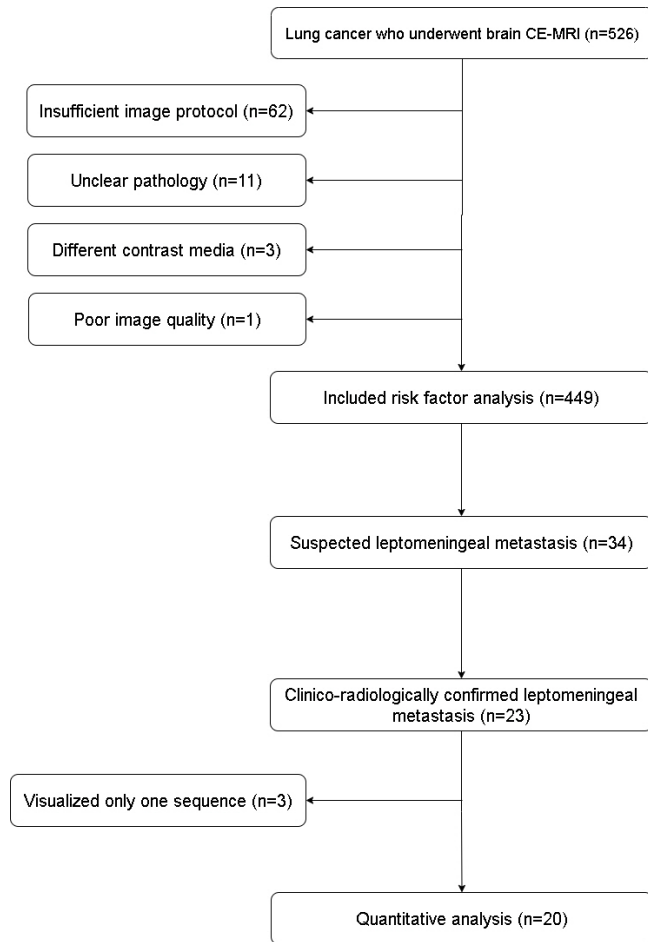


Fig. 1. Flow chart of study design. We found 526 patients with lung cancer who underwent brain CE-MRI. Of these, we excluded 77 patients, and considered 449 patients to be eligible for risk-factor analyses. Of the 449 patients, we selected 34 participants in whom leptomeningeal metastasis was suspected for qualitative analysis. Among them, 23 patients were finally diagnosed to have true leptomeningeal metastasis. Among the 23 confirmed participants, we excluded 3 patients because the lesions were visualized on only one image sequence. Finally, we considered 20 patients to be eligible for quantitative analyses.

a period of two weeks was taken after each session. After all sessions, we obtained the inter-observer agreements using the results of the two readers; if the results of the two readers were different, the third subspecialty-trained radiologist (J.Y.K., 7 years of experience) made a final conclusion with a blind review. We calculated the diagnostic performances based on this final conclusion.

We did quantitative analyses on the MR images of 20 confirmed LM patients who demonstrated lesions on both CE-T1WI and CE-T2 FLAIR images. We defined it as

comparing the SNR and CNR obtained from drawing ROIs on LM lesions simultaneously identified in CE-T2 FLAIR and CE-T1WI. We calculated the signal-to-noise ratio (SNR) and the contrast-to-noise ratio (CNR) using the formula; $SNR = SI_{lesion}/(SI_{lesion})^{1/2}$, $CNR = (SI_{lesion} - SI_{GM})/(SI_{lesion})^{1/2}$ (15).

We drew lesion ROIs on the most obvious leptomeningeal lesion in all images, using the semi-automatic segmentation method (Nordic ICE; Nordic NeuroLab, Bergen, Norway). In addition, we obtained the mean signal intensity of gray matter (ipsilateral thalamus) with 60-mm² circular ROI. The example of ROI placement is attached in Supplementary Figure 1.

Clinical Data Acquisition

We reviewed the electronic medical records of 449 patients and obtained age, gender, cell type of lung cancer, and purpose of imaging study (initial staging/re-staging) at the time of imaging. For initial radiologic lung-cancer staging, since the American Joint Committee on Cancer (AJCC) 7th and 8th editions were being revised during the study period, we did re-staging according to the 8th edition based on the radiographic report obtained during daily practice.

Statistical Analysis

To evaluate the benefits gained by the MR image study, we calculated the detection rate in the MR-screen group (DR). We defined the DR as the number of patients who showed true LM among the MR-screen group (number of true positive divided by the number of MR-screen patients). In qualitative analyses, we evaluated the diagnostic performances of CE-T1WI, CE-T2 FLAIR, and combined analysis in terms of sensitivity, specificity, and accuracy. We did the receiver operating characteristic (ROC) curve analysis to compare the diagnostic performance between the image analysis sessions. We used the DeLong test to compare the calculated AUCs. We calculated the Cohen's kappa value to assess inter-rater reliability. In quantitative analyses, we compared the mean SNR and CNR obtained from the same lesion in CE-T1WI and CE-T2 FLAIR using the Wilcoxon signed rank test. We did the risk-factor analysis using logistic regression corrected for the initial radiologic lung-cancer stage for patient's age, gender, MR machine, cell type of lung cancer, presence of brain metastasis, and purpose of study (initial staging/re-staging). At this time, instead of the corrected P value used for multiple comparisons, we considered $P < 0.05$ to indicate a statistically significant difference in the exploratory

setting. Then, we used multivariate logistic regression on the significant risk factors. We did statistical analyses using MedCalc 18.2.1 (MedCalc Software, Belgium). We considered $P < 0.05$ to indicate a statistically significant difference.

RESULTS

Demographic and Clinical Data

Of the 449 patients, 34 patients were clinico-radiologically suspected to have LM. We diagnosed 23 of them as having true LM; the DR was 5.1% (23/449). The demographic and clinical characteristics of the study

Table 1. Demographics and Clinical Data

Variables	All participants (n = 449)	Qualitative analysis (n = 34)	Quantitative analysis (n = 20)
Age	67.3 ± 10.9	65.0 ± 10.0	65.3 ± 9.9
Gender	325/124	23/11	12/8
MRI machine (Signa HDx/Skyra)	310/139	22/12	13/7
Initial stage ^{a)}			
cl	47	1	0
clI	24	2	1
clII	131	4	1
clIV	232	27	18
Clinical T stage ^{b)}			
T1	67	4	0
T2	96	6	3
T3	52	3	3
T4	207	18	11
Clinical N stage ^{c)}			
N0	97	8	3
N1	47	3	1
N2	86	2	2
N3	212	19	12
Clinical M stage ^{d)}			
M0	214	7	2
M1	232	27	18
Purpose of study (initial staging/re-staging)	118/331	10/24	6/14
Parenchymal metastasis (present/absent)	91/358	17/17	14/6
Lung cancer cell type			
Adenocarcinoma	249	23	17
Other NSCLC ^{e)}	150	6	2
SCLC ^{f)}	50	5	1

All data are numbers; mean data are ± standard deviation. Initial and TNM stage (T for tumor, N for lymph nodes, and M for distant metastasis) for lung cancer were based on the AJCC 8th edition. Initial stage^{a)}. We excluded 15 participants for unavailability of data. In clinical T-stage^{b)}, we excluded 27 of all participants, 3 from qualitative analysis, and three from quantitative analysis because the data were not available. In clinical N stage^{c)}, we excluded seven from all participants, two from qualitative analysis, and two from quantitative analysis. In clinical M^{d)} stage, we excluded three participants from the all-participants group because of unavailable data. Other NSCLC^{e)} included squamous-cell carcinoma (n = 125), non-small-cell lung cancer, not otherwise specified (n = 11), large-cell neuroendocrine carcinoma (n = 11), adenosquamous carcinoma (n = 1), atypical carcinoid (n = 1), and malignant spindle-cell carcinoma (n = 1). SCLC^{f)} refers to small-cell lung cancer.

MRI = magnetic resonance imaging; NSCLC = non-small-cell lung carcinomas; SCLC = small-cell lung cancer

participants are summarized in Table 1. In the cases by MRI machine, Signa HDx was higher than that of Skyra in all participants, qualitative, and quantitative analysis groups. In the initial clinical staging, cIV was the most common in all three groups. The purpose of MR examination was that the initial metastasis work-up studies were more frequent than was re-staging in all participants. In contrast, in the qualitative and quantitative analysis group, the number of re-stagings was higher. Brain parenchymal metastasis was 20.6% in the total patient group, but higher in the qualitative and quantitative analyses groups (50%, 70%, respectively). In the total patient group, adenocarcinoma ($n = 249$) was the most common cell type, followed by other non-small-cell lung carcinomas (NSCLCs, $n = 150$) and small-cell lung cancer (SCLC, $n = 50$). In the group where qualitative and quantitative analyses were conducted, adenocarcinoma was also the most common ($n = 23$, 17, respectively).

Table 2. Diagnostic Performance and Inter-observer Agreement in Qualitative Analysis

Suspected LM ^{a)} ($n = 34$)	LM (+) ^{b)}	LM (-) ^{c)}	Total
CE-T1WI ^{d)} (+)	20	3	23
CE-T1WI ^{d)} (-)	3	8	11
CE-T2 FLAIR ^{e)} (+)	21	3	24
CE-T2 FLAIR ^{e)} (-)	2	8	10
Combined ^{f)} (+)	22	2	24
Combined ^{f)} (-)	1	9	10
Diagnostic performance (%)	Sensitivity	Specificity	Accuracy
CE-T1WI ^{d)}	87.0	72.7	82.4
CE-T2 FLAIR ^{e)}	87.5	80.0	90.0
Combined ^{f)}	91.7	90.0	91.2
Inter-observer agreement (Cohen's kappa, 95% confidence interval)			
CE-T1WI ^{d)}	0.68 (0.42 - 0.93)		
CE-T2 FLAIR ^{e)}	0.72 (0.46 - 0.98)		
Combined ^{f)}	0.86 (0.67 - > 0.99)		

Suspected LM^{a)} refers to suspected leptomeningeal metastasis (LM) patients. LM (+)^{b)} refers to patients who were finally diagnosed to have true LM. LM (-)^{c)} refers to patients who were finally diagnosed as not having LM. CE-T1WI^{d)} refers to the image analysis session in which LM was evaluated using only a contrast-enhanced 3D T1 black-blood fast spin-echo image. CE-T2 FLAIR^{e)} refers to the image analysis session in which LM was evaluated using only a contrast-enhanced 2D T2 fluid-attenuated inversion recovery image. Combined^{f)} refers to the evaluation of LM by reviewing CE-T1WI and CE-FLAIR together in one image analysis session. CE-T1WI = contrast-enhanced T1 weighted image; CE-T2 FLAIR = contrast-enhanced T2 fluid-attenuated inversion recovery; LM = leptomeningeal metastasis

Qualitative Analysis ($n = 34$)

The diagnostic performances calculated for each session are summarized in Table 2. The sensitivity, specificity, and accuracy were the best in all the combined analyses. The combined analysis (0.89, confidence interval [CI]: 0.73-0.97) showed a larger AUC than did CE-T1WI (0.80, CI: 0.63-0.92) or CE-T2 FLAIR (0.82, CI: 0.65-0.93). However, this difference was not statistically significant (DeLong test, $P > 0.05$) (Fig. 2). For the inter-observer agreement calculated for each session, CE-T1WI and CE-T2 FLAIR were substantial (0.68, 0.72, respectively), and the combined analysis was perfect (0.86).

Quantitative Analysis ($n = 20$)

According to the quantitative analysis of the 20 patients with confirmed LM and in whom LM lesions in both images were observed, the SNR of CE-T2 FLAIR was significantly higher than that of CE-T1WI (Median and interquartile range were 32.1, 27.0-36.5 and 26.1, 22.1-27.8, respectively; $P < 0.001$). For the CNR, the measurements from CE-T2 FLAIR were significantly higher than those of CE-T1WI (Median and interquartile range were 10.6, 6.4 - 14.5 and 6.8, 3.8 - 8.8, respectively; $P < 0.01$) (Table 3). In the dot-and-line graph, CE-T2 FLAIR showed higher SNR

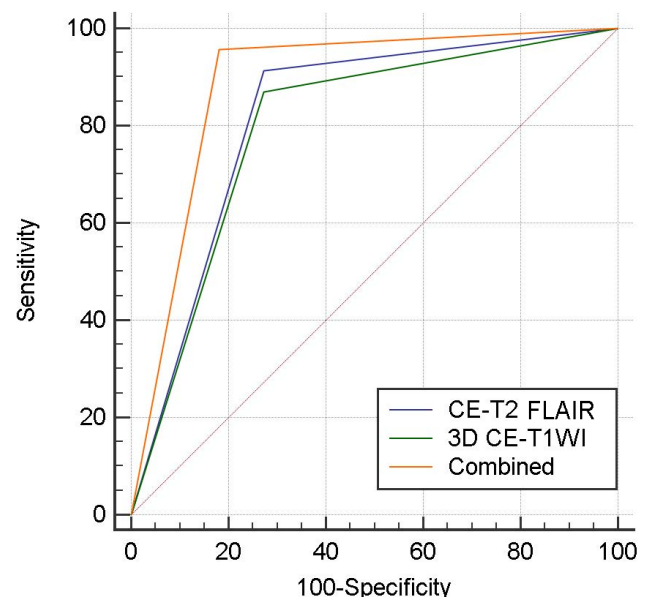


Fig. 2. Receiver operating characteristic (ROC) curve of qualitative analyses. On the ROC curve analysis, the combined analysis (0.89, confidence interval [CI]: 0.73-0.97) showed a larger AUC than did CE-T1WI (0.80, CI: 0.63-0.92) or CE-T2 FLAIR (0.82, CI: 0.65-0.93). However, this difference was not statistically significant (DeLong test, $P > 0.05$).

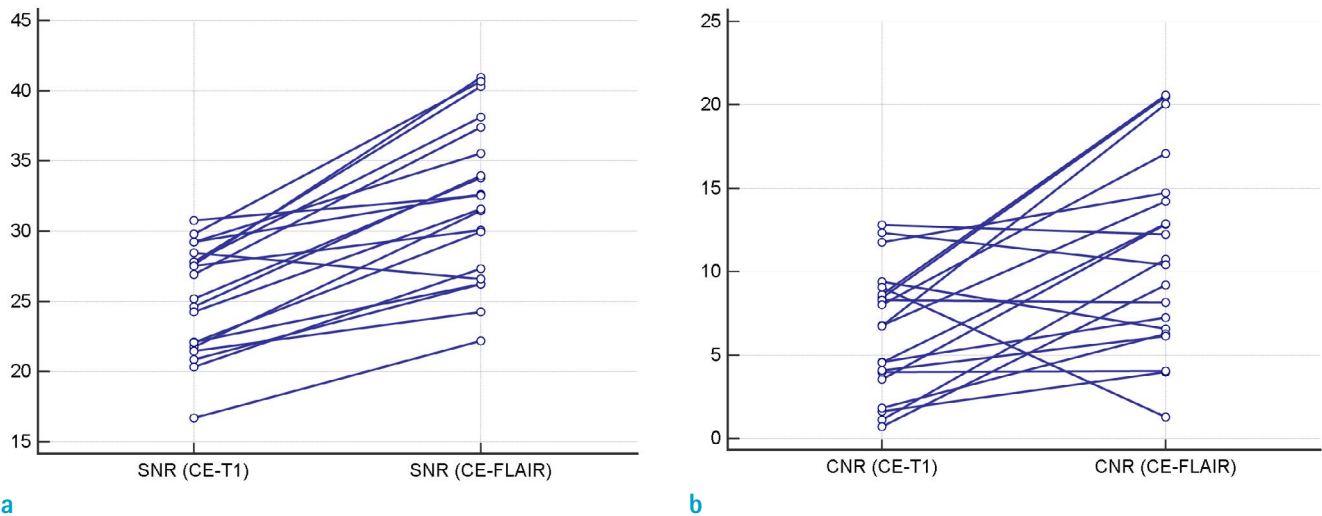


Fig. 3. Dot-and-line graph of quantitative analyses. (a) Calculated signal-to-noise ratio (SNR) (b) calculated contrast-to-noise ratio (CNR). Each dot represents a measurement. In the SNR and CNR measured in paired leptomenigeal lesions on each image, almost all measurements from CE-T2 FLAIR were higher than those from CE-T1WI. However, in one case from SNR and in four cases from CNR, the measured value of CE-T1WI was higher than that of CE-T2 FLAIR.

Table 3. Measured SNR and CNR in Quantitative Analyses (n = 20)

	CE-T1WI ^(a)	CE-T2 FLAIR ^(b)	P-value ^(c)
SNR ^(d) (inter quartile range)	26.06 (21.92 - 28.14)	32.06 (26.97 - 36.47)	< 0.001
CNR ^(e) (inter quartile range)	6.75 (3.76 - 8.58)	10.57 (6.42 - 14.47)	< 0.01

CE-T1WI^(a) refers to the mean value measured on a contrast-enhanced 3D T1 black-blood fast spin-echo image. CE-T2 FLAIR^(b) refers to the mean value measured on a contrast-enhanced 2D T2 fluid-attenuated inversion recovery image. Each P value^(c) was obtained through the Wilcoxon signed rank test. SNR^(d) refers to the signal-to-noise ratio and was calculated as $SNR = S_{lesion}/(S_{lesion})^{1/2}$. CNR^(e) refers to the contrast-to-noise ratio and was calculated as $CNR = (S_{lesion} - S_{GM})/(S_{lesion})^{1/2}$.

CE-T1WI = contrast-enhanced T1 weighted image; CE-T2 FLAIR = contrast-enhanced T2 fluid-attenuated inversion recovery; CNR = contrast-to-noise ratio; LM = leptomenigeal metastasis; SNR = signal-to-noise ratio

than did CE-T1WI in all lesions except in one case and higher CNR in almost lesions except for four cases (Fig. 3).

Risk-factor Analysis

Given the risk-factor analysis conducted in the 449 patients, the significant factors for predicting LM in logistic regression corrected by initial lung-cancer stage were the presence of brain parenchymal metastasis, the re-staging, and adenocarcinoma cell type. There was no significant difference in the age, gender, performed MR machine, SCLC, or other NSCLC cell types. The results of multivariate analyses, including three significant factors, the presence of

brain metastasis, and the follow-up study, were statistically significant, but the adenocarcinoma cell type was not ($P = 0.069$). The calculated odds ratios for each risk factor are summarized in Table 4. The DR for each of the three risk factors was 15.3% (18/118) in the re-staging study, 17.6% (16/91) in the presence of brain parenchymal metastasis, and 8.0% (20/249) in the adenocarcinoma cell type.

DISCUSSION

In this study, the overall DR for LM was 5.1% (n = 23/449). The qualitative analyses revealed that both conferred the best performance. Moreover, in inter-observer agreement, the combined analysis was the best. In quantitative analyses, CE-T2 FLAIR showed significantly higher SNR and CNR than did CE-T1WI for the same lesion. In the risk-factor analysis, there was no difference according to the MR machine, but LMs were more frequently observed in the presence of brain parenchymal metastasis, re-staging study, and the adenocarcinoma cell type.

The CE-T2 FLAIR image has been expected to be used for the detection of LM based on the MR physics that CE-T2 FLAIR shows a higher signal intensity than do variants of T1WI when the gadolinium concentration is low (16, 17). Indeed, some previous studies have reported that CE-T2 FLAIR was helpful in the diagnosis of LM (6, 8). However, most of these publications were conducted as research-

Table 4. Risk Factor Analyses (n = 449)

Variables	Stage-adjusted logistic regression		Multivariate	
	Odd ratio (95% CI)	P-value	Odd ratio (95% CI)	P-value
Age	0.99 (0.95 - 1.03)	> 0.05		
Sex (Female)	1.98 (0.81 - 4.86)	> 0.05		
MR machine (Signa HDx)	0.70 (0.29 - 1.71)	> 0.05		
Cell type				
Other NSCLC	Ref		Ref	
Small cell carcinoma	3.40 (0.29 - 40.26)	> 0.05	2.75 (0.23 - 33.33)	> 0.05
Adenocarcinoma	8.41 (1.04 - 67.86)	< 0.05	6.83 (0.86 - 54.31)	= 0.069
Parenchymal metastasis (Present)	4.33 (1.45 - 12.90)	< 0.001	5.22 (1.95 - 14.00)	< 0.01
Study purpose (Re-staging)	9.71 (3.38 - 27.88)	< 0.001	7.76 (2.68 - 22.49)	< 0.01

CI = confidence interval; other NSCLC = non-small-cell lung cancer except adenocarcinoma and small-cell carcinoma; Ref = reference

based studies, and therefore little is known about how many patients actually benefited when CE-T2 FLAIR was applied in the real-world setting. Therefore, our study can provide data on the clinical gain when the CE-T2 FLAIR image is added in lung-cancer staging/re-staging and can help to guide the decision on whether to invest additional time in the image protocol.

Since the CNR and SNR were relatively high in almost all cases, the CE-T2 FLAIR worked well in the detection of LM (Fig. 4). However, a pseudo-lesion caused by cortical contrast retention can interfere with the correct diagnosis (6). In addition, since 2D CE-FLAIR was added in our study, there were limitations, in that the morphology of lesions should be evaluated in only one plane, and the reduction of z-axis resolution resulted from the 5-mm slice thickness with 1-mm gap. This was particularly noticeable in the detection of LM along the CN. In fact, one of the two false-negative cases of CE-T2 FLAIR was one in which LM appeared only as CNS involvement. This lesion was not detected in the analysis using only CE-T2 FLAIR, but was relatively well observed in the CE-T1WI (Fig. 5). Moreover, interestingly, even for the LM observed along the cerebral cortical sulci, there were few cases where CE-T1WI was clearly seen compared to CE-T2 FLAIR (Fig. 6). Indeed, in the quantitative analyses results, the CNR was measured higher in four cases. In contrast, CE-T1WI visualized almost all LM, but since it was relatively subtler than CE-T2 FLAIR, detection was time-consuming and inter-observer agreement was low. In addition, since we could not use techniques to suppress vascular signals (DANTE or iMSDE), it was difficult to exclude pseudo-positive lesions caused

by cortical vessels, which are indicated as limitations in the CE-T1WI (18). In particular, for LM, there are few diagnostic methods except for MR images (19); if only one image is suspected, there is a difficulty in making invasive medical decisions, such as whole-brain radiation therapy or intrathecal chemotherapy. However, when two images are combined, an inter-observer agreement could be raised, and excluding artifacts from each image helps in decision making. Furthermore, the adding of CE-T2 FLAIR before CE-T1WI scan lengthened the contrast-to-image time for CE-T1WI in the metastasis work-up. Previous studies on metastasis detection have reported that the detectability of metastatic lesions increased as the time delay between contrast injection and T1WI acquisition increased (20, 21). However, in clinical practice, the longer delay time increases the scan time, thereby reducing the scanner through output and increasing the patient's inconvenience (22). In particular, having the patient wait in the MR machine without imaging may be considered to be a waste of medical resources. However, if you add CE-T2 FLAIR, you can save some minutes before T1WI.

Unfortunately, the relative infrequency of LM is an obstacle to adding this image to the routine protocol. In this study, the LM was more frequently detected when there was brain parenchymal metastasis, the imaging purpose was re-staging, and the cell type was adenocarcinoma. In a study conducted on 519 patients with LM, prior/current CNS metastasis was reported to have been 70%, the primary tumor's median duration at the time of detection was 18 months, and the largest number of primary tumors were lung cancer, 95% of which was adenocarcinoma

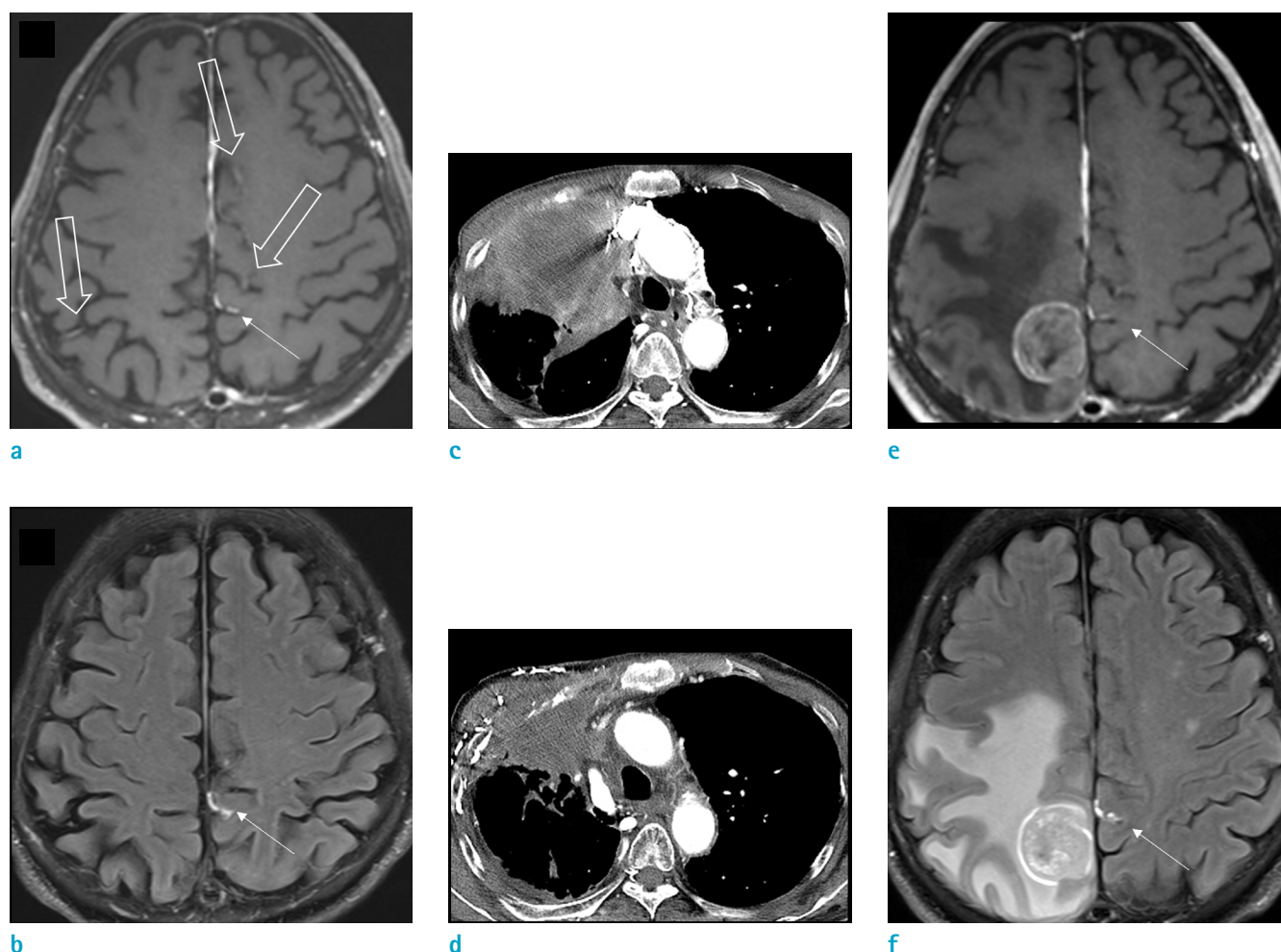


Fig. 4. Representative case. A 76-year-old man with lung cancer (adenocarcinoma, initial stage cIIIC except for leptomenigeal metastasis). On initial brain CE-MRI, (a) several curvilinear high signal intensities were noted along the cerebral cortical sulci (arrow and open arrows) on CE-T1WI (measured SNR, CNR from arrow: 22.1, 4.5, respectively). (b) On CE-T2 FLAIR only one lesion was correlated, so we presumed that the lesion was suspected leptomenigeal metastasis (measured SNR, CNR on arrow: 30.3, 12.9, respectively). (b) On CE-T2 FLAIR only one lesion (arrow) was correlated, so we presumed that the lesion was suspected leptomenigeal metastasis (measured SNR, CNR on arrow: 30.3, 12.9, respectively). However, since there were no correlated neurologic symptoms at that time, the patient received radiation treatment only for the lung lesion and started palliative chemotherapy. After three months, the size of the lung lesion was reduced on re-staging (c, d), but on brain CE-MRI (e, f, not included in the study), the leptomenigeal lesion was still observed (arrows) and a new brain metastasis was noted. We finally diagnosed this case as leptomenigeal metastasis. He underwent radiation treatment for these brain lesions with palliative chemotherapy and is still alive, 27 months from initial diagnosis.

(23). In a study of 205 patients with LM published in 2018, the median duration was 13 months, with pulmonary adenocarcinoma most common, at 52% (14); these data corroborate the findings of our study. In this previous study, LM had an initial manifestation in 19 patients, with 12% of the total; among them, 74% of the cases were pulmonary adenocarcinoma. In our study, of the 23 confirmed patients with LM, five (21.7%) were detected at the time of initial

staging, and four of them had adenocarcinoma. The rate of detection during the initial staging was relatively larger in our study, but the ratio of adenocarcinoma was similar. In contrast, in the previous studies about DY, for brain CE-MRI done during initial metastasis work-up for lung cancer, the diagnostic yield (DY) was approximately 11.9% in NSCLC (24). In contrast, the DY of chest and abdomen computed tomography (CT) and/or positron emission tomography/

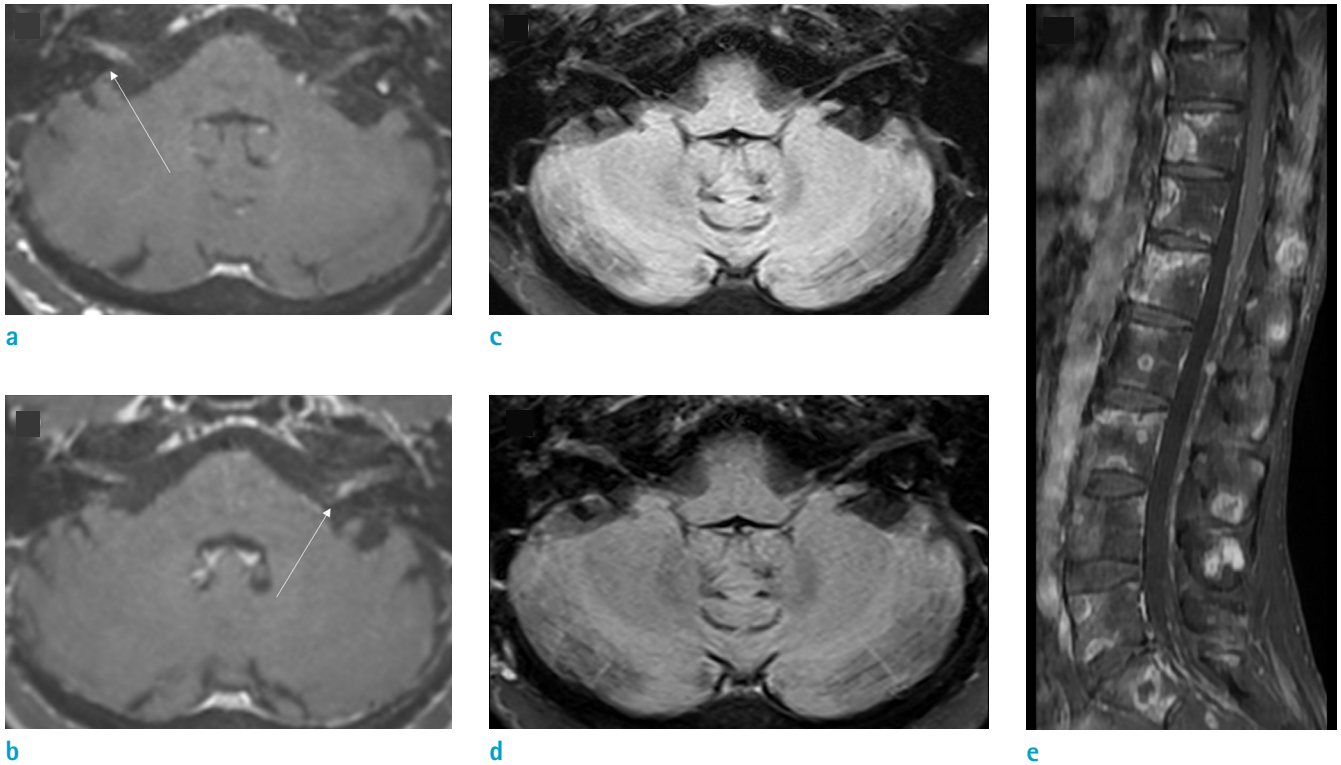


Fig. 5. Limitation of 2D CE-T2 FLAIR (lesions along the cranial nerves). A 51-year-old man with lung cancer (adenocarcinoma, initial stage cIVb, re-staging). (a, b) On CE-T1WI, we noted tiny nodular enhancing lesions along both cranial nerves 7/8 (arrows). However, on CE-T2 FLAIR (c, d), the corresponding enhancing lesion did not visualize well. This patient underwent whole neuroaxis radiation therapy, because concurrent leptomeningeal metastasis was confirmed on spine CE-MRI (e) performed 8 days later.

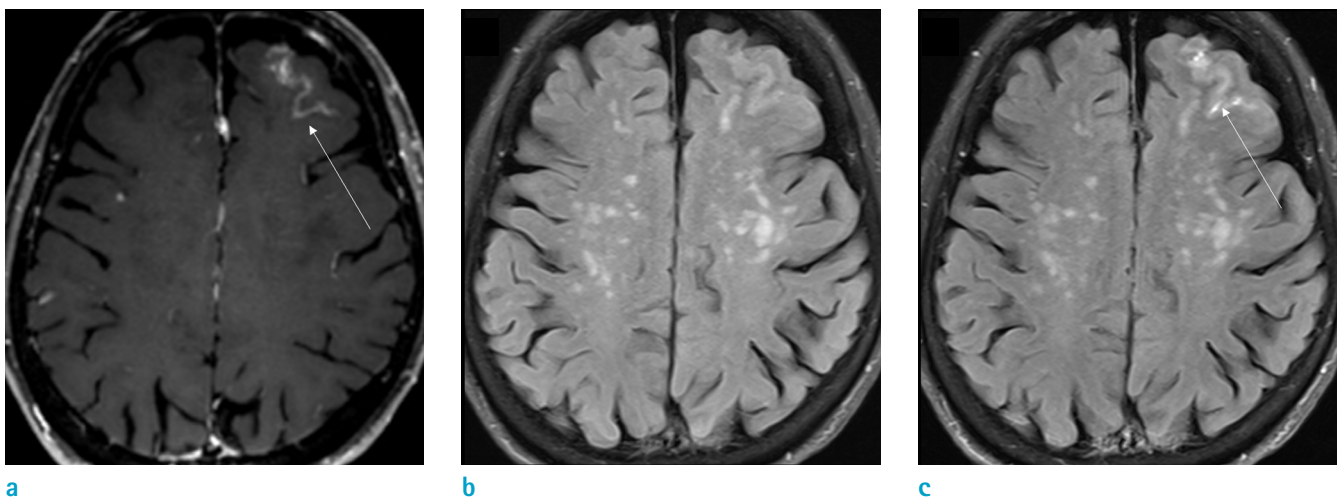


Fig. 6. An exceptional case that was better visualized on CE-T1WI than on CE-T2 FLAIR. An 83-year-old woman with lung cancer (adenocarcinoma, initial stage cIVb, re-staging) CE-T1WI (a) showed a high signal intensity lesion along the left frontal cortical sulci (arrow, SNR: 20.9, CNR: 9.4). This lesion was correlation on CE-T2 FLAIR (b, c), but was relatively less conspicuous (arrow, SNR: 26.2, CNR: 6.6). The patient was diagnosed to have leptomeningeal metastasis based on diagnostic imaging features with neurologic symptoms (headache, dizziness) and was treated with whole-brain radiation therapy.

CT (PET/CT) in primary CNS lymphoma was 2% (25). In our study, we found about 5.1% patients with LM; the DR for each risk factor was 17.6% for the presence of brain parenchymal metastasis, 15.3% for re-staging, and 8.0% for adenocarcinoma cell type. Such data are expected to help one decide whether to add about 3–4 min of CE-T2 FLAIR without a radiation hazard when applied to each institutional situation.

This study has several limitations. First, the image analysis in this study was performed only on selected suspected cases, instead of all scanned MR images used in calculating DR and risk factors. For this reason, there may be false-negative cases that were not clinically suspected among patients whose image review consisted only of radiologic reports, and there may have been selection bias in suspected cases ($n = 34$) selected for qualitative analysis. However, for DR and risk-factor analysis, in a previous study evaluating the DY (25) in a way like that used this study, a group of patients to evaluate true positive and true negative was selected using radiographic reports obtained from routine clinical practice, instead of by reviewing all images. In addition, enrolled participants were the patients who underwent lung-cancer management at our institution; we knew their life expectancy was relatively short (14, 23). Therefore, we assumed that the number of possible false-negative cases would not have a significant effect on our results. Despite this limitation, the DR and risk-factor analysis of this study may be used as reference values for studies to be conducted for the clinical application of CE-T2 FLAIR in the future or for institutions considering CE-T2 FLAIR for clinical application. Therefore, we used the term DR instead of DY to prevent overestimation of the result. The data in this study need to be confirmed by a future cohort study conducted in a representative group.

Second, not all our study subjects had a cytological diagnosis, which may result in false positives or false negatives in our results. However, CSF cytology is difficult to apply in all patients, because its sensitivity is lowered by the procedure's invasiveness (26, 27). Therefore, we used as diagnostic criteria the combination of cytology, MR imaging, and clinical symptoms used in previous studies (12–14). In addition, a neuro-oncologist, who could access the follow-up clinical and image data until the study point, decided on the final diagnosis, thus minimizing the effect of these biases on the results.

Third, our study had only a few participants, was conducted with only one contrast medium on two MR machines, and was a single center study. Hence we had only

a few patients with LM, which could result in insufficient statistical power in risk-factor analyses. Furthermore, the effect analysis by different types of contrast media and MR machines was limited. However, research on LM is not easy, because of its relatively low incidence and its reduced life expectancy (14, 23). These results should be confirmed by future studies on larger scales.

Fourth, CE-T2 FLAIR was scanned before CE-T1WI. There is not much research on the optimal time of CE-T2 FLAIR for metastasis detection. A study evaluating metastasis detection reported that there was no significant difference in diagnostic performance between delayed CE-T2 FLAIR images (28). In our study, we decided to scan CE-T2 FLAIR first at the time of study design because CE-T1WI was essential for parenchymal metastasis evaluation (18). However, since this study was not about optimal image-acquisition time for CE-T2 FLAIR, the assessment should be addressed in other future studies.

In conclusion, adding CE-T2 FLAIR may add diagnostic value in the detection of LM in the brain-metastasis screening for lung cancer by improving the visibility and inter-observer agreement. CE-T2 FLAIR showed a PR of about 5.1% in lung-cancer metastasis work-up, which was higher in the presence of brain parenchymal metastasis, re-staging, and adenocarcinoma cell type.

Supplementary Materials

The Table Supplements are available with this article at <https://doi.org/10.13104/imri.2022.26.1.32>

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