ORIGINAL ARTICLE

Leptomeningeal enhancement in magnetic resonance imaging predicts poor prognosis in lung adenocarcinoma patients with leptomeningeal metastasis

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Abstract

Background: To investigate the prognostic value of magnetic resonance imaging (MRI) findings in the prognosis of patients with leptomeningeal metastasis from lung adenocarcinoma.

Methods: Patients with lung adenocarcinoma complicated with cytologically confirmed leptomeningeal metastasis who visited Peking Union Medical College Hospital (blinded for review) between January 2012 and July 2019 were retrospectively reviewed. We collected the patients' clinical and neuroimaging findings and pathological data. The presence of leptomeningeal enhancement on initial contrast MRI was used to divide patients into MRI-positive and MRI-negative groups. Univariate and multivariate analyses were performed to evaluate prognostic factors.

Results: Eighty-six patients (38 men and 48 women; median age = 56 [range, 25–80]) were included. Seventy-three patients (84.9%) had targetable genetic alterations. Only 30 patients (34.88%) had leptomeningeal enhancement on initial contrast MRI. No significant differences were observed in the distribution of demographics, driver gene status, intracranial pressure, complicated brain/spinal metastasis, or treatment strategies between the two groups. The median overall survival of patients in the MRI-positive group was significantly shorter than that in the negative group (182 days vs. 352 days, $p = 0.036$). Cox regression analysis indicated that the presence of leptomeningeal enhancement on the initial diagnostic magnetic resonance imaging was an independent predictor of an unfavourable prognosis of leptomeningeal metastasis (hazard ratio = 1.707, $p = 0.044$).

Conclusions: This is the first time that positive initial contrast-enhanced magnetic resonance imaging of the neuroaxis has been proposed as a risk factor for the prognosis of leptomeningeal metastasis from lung adenocarcinoma with contemporary survival data.

KEYWORDS
adenocarcinoma of lung, magnetic resonance imaging, meningeal carcinomatosis, prognosis

INTRODUCTION

Lung carcinoma is one of the most common malignancies leading to mortality and morbidity worldwide. Leptomeningeal metastasis (LM) is a devastating complication that occurs in 1%–5%[1,2] of patients diagnosed with non-small cell lung cancer (NSCLC), with an estimated overall survival (OS) of 4–6 weeks if left untreated.[3,4] The conventional diagnosis of LM is based on neurological signs or symptoms, imaging of the neuroaxis, and cerebrospinal fluid (CSF) examination. Neuroimaging is

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important and is usually the first diagnostic step upon suggestive clinical presentations of LM, although tumor cells revealed using CSF cytology remain the gold standard for diagnosing LM. Since the diagnostic sensitivity of a single CSF cytology test is merely 50%–65%,[5–7] contrast-enhanced magnetic resonance imaging-identified LM combined with typical neurological presentations could establish a diagnosis of probable LM,[8] as classified by the European Association of Neuro-Oncology-European Society for Medical Oncology (EANO-ESMO). Contrast magnetic resonance imaging (MRI) of the neuroaxis is the most recommended imaging tool for identifying leptomeningeal metastases, in which LM leads to a pathological enhancement of the leptomeninges of the brain, spinal cord, cranial nerves, and brain ventricles that are involved in CSF circulation. LM enhancement is classified as nodular (defined as less than 5 mm) or linear/curvilinear; focal or diffuse.[9] Nevertheless, up to 24% of patients with LM are reported to have no leptomeningeal enhancement or normal contrast MRI.[10,11] It is a question for clinical oncologists as to whether patients with LM with positive contrast-enhanced MRI findings are different from those without. Moreover, for patients without leptomeninges enhancement on contrast MRI, how can we identify them as potential LM patients and recommend they undergo further CSF cytology examinations? Several clinical questions need to be answered.

Because of poor clinical outcomes, there have been many studies on LM from lung cancer or from lung cancer in combination with other solid tumors; these studies have revealed LM-related clinical features, administration of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), and other active treatments as prognostic factors.[4,12,13] Beginning in 2017, neuroimaging has been utilized in the stratification of LM, as suggested by the first guideline on LM from EANO-ESMO.[8] The LM enhancement patterns along with CSF cytology results were shown to be prognostic indicators based on data from solid tumors, including lung cancer.[14] Our long-term research program and exploration of LM in patients with NSCLC[15] helped to establish a continuous study cohort. In this cohort, we observed positive initial neuroaxis imaging findings which might be associated with poor prognosis in patients with leptomeningeal lung adenocarcinoma, the major histopathological subtype of the LM population.[12,16–18] In this retrospective study, we aimed to explore the prognostic value of initial MRI in patients diagnosed with lung adenocarcinoma with LM. Furthermore, we also aimed to identify neuroimaging features that might be useful for early identification of LM in patients without leptomeningeal enhancement.

METHODS

Patients

All patients with LM derived from lung adenocarcinoma who visited Peking Union Medical College Hospital (blinded for review) between January 2012 and July 2019 and met the following inclusion criteria were enrolled in the study. The inclusion criteria were as follows: (1) a histologically or cytologically confirmed diagnosis of lung adenocarcinoma; (2) upon neurological signs and symptoms, patients who underwent contrast-enhanced MRI and CSF testing (the time interval between these two examinations was less than two weeks); and (3) a diagnosis of LM confirmed using CSF cytology (type I LM according to the EANO-ESMO classification).[8] Eligible patients were further divided into two groups according to the presence or absence of leptomeningeal enhancement on initial contrast-enhanced MRI.

Driver gene detection

Detection of genetic alterations at primary tumor sites, such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangement, cellular-mesenchymal to epithelial transition factor (c-MET) amplification, and ROS proto-oncogene 1 (ROS1) rearrangements were acquired using state-of-the-art methods, including the amplification refractory mutation system, fluorescence in situ hybridization, and next-generation sequencing.

Contrast MRI and its interpretations

Qualified gadolinium-containing contrast (dosage of gadopentetate dimeglumine: 0.1 mmol per kg bodyweight) MRI was performed using a General Electric MRI scanner (3.0 T 8 channal phasearray). Sequences of axial T1-weighted, axial T2 and T2*-weighted, axial diffusion, and post-gadolinium axial/sagittal/coronal T1-weighted sequences were obtained from a contrast brain MRI. Contrast spine MRI was conducted at the physician's discretion, which included spinal sagittal T1-weighted, T2-weighted fat suppression, and post-gadolinium sagittal T1-weighted sequences. The slice thickness was 5 mm with a 1-mm interval. Each set of contrast-enhanced MRI scans was reviewed by two independent radiologists. Characteristic MRI findings included sulcal and folial enhancement or obliteration, linear ependymal and cranial nerve root enhancement, and leptomeningeal enhancing nodules, notably of the cauda equine.[5] Pathological enhancement patterns were nodular, linear, or curvilinear.[9] Complicated parenchymal brain/spinal metastases and the presence of hydrocephalus were also investigated.

CSF findings

CSF samples were acquired from all patients for intracranial pressure (ICP) data and CSF cytology tests. Normal ICP was within the range of 80–180 mm H_2O. CSF

cytology was performed using the natural precipitation method or liquid-based cytology test and examined by two independent pathologists.

Data collection and statistical analyses

Patient demographics, clinical data, laboratory results, imaging findings, and survival information were collected from the databases of an observational study of Chinese patients with NSCLC with LM (NCT02803619) and an observational cohort study of patients with advanced NSCLC (CAPTRA-Lung, NCT03334864). Patients whose date of death was not recorded or when no information was obtained at follow-up phone calls were censored at the date of the last follow-up. This study was approved by the Ethics Committee of Peking Union Medical College Hospital and all participants gave their informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Quantitative parameters were presented as median and interquartile range (IQR) (25–75th percentiles) or range if specifically indicated, and qualitative parameters were presented as number and percentage. Statistical analyses were conducted using SPSS software (version 22.0). OS was calculated from the date of the confirmed cytological diagnosis of LM to the date of death. To demonstrate the timing of cytology, two indicators were employed and compared using the Mann–Whitney U test between MRI positive and negative groups: the interval between suggestive neurological signs/symptoms and cytological diagnosis of leptomeningeal metastasis; the interval between initial MRI of neuroaxis and cytological diagnosis of leptomeningeal metastasis (shown in Figure S1). All potential risk factors were binary variables and were compared between MRI positive group and MRI negative group using Fisher's exact test and Chi-square tests. In the univariate analysis, survival was estimated using the Kaplan–Meier curve and was compared using the log-rank test between groups. Multivariate analysis was performed using the Cox proportional hazards model. Statistical significance was set at $p < 0.05$.

RESULTS

Clinical characteristics of patients

A total of 86 patients (38 men and 48 women) were included in this retrospective study. The median age at the diagnosis of LM was 56 (range, 25–80) years. Ever-smokers accounted for 30.2% of the patients ($n = 26$). A prominent majority (73, 84.9%) of patients had targetable mutations: there were 69 cases with *EGFR* mutations (including three patients with concurrent c-MET amplification) and four with ALK rearrangement (Figure S2). It was hard to accurately evaluate patient performance status since it was easily and evidently affected by administration of dehydration and antitumor agents.

TABLE 1 Characteristics of initial and follow-up contrast MRI findings

	Distribution of LM			Patterns of LM			Characteristics of LM		Hydrocephalus	Concurrent brain/spine parenchyma metastasis
	Brain pia mater enhancement only	Spinal pia mater/nerve root enhancement only	Both brain and spinal pia mater enhancement	Linear/curvilinear enhancement only	Nodular enhancement only	Both linear/curvilinear and nodular enhancement	Focal	Diffuse		
All patients, initial MRI (N = 86)	26 (30.23%)	1 (1.16%)	3 (3.49%)	16 (18.60%)	4 (4.65%)	10 (11.63%)	4 (4.65%)	26 (30.23%)	30 (34.88%)	52 (60.47%)
MRI positive group initial MRI (N = 30)	26 (86.67%)	1 (3.33%)	3 (10.00%)	16 (53.33%)	4 (13.33%)	10 (33.33%)	4 (13.33%)	26 (86.67%)	16 (53.33%)	17 (56.67%)
MRI negative group initial MRI (N = 56)	-	-	-	-	-	-	-	-	14 (25.00%)	35 (62.50%)
Subgroup A follow-up MRI (N = 16)	13 (81.25%)	3 (18.75%)	-	9 (56.25%)	0	7 (43.75%)	4 (25%)	12 (75%)	6 (37.50%)	11 (68.75%)

Abbreviations: LM, leptomeningeal metastasis; MRI, magnetic resonance imaging.
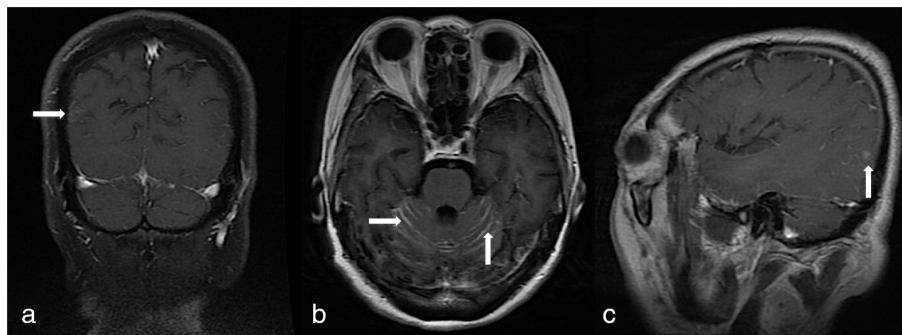
FIGURE 1 Different patterns of leptomeningeal enhancement on contrast magnetic resonance imaging. (a) A focal lesion with linear/curvilinear enhancement in the right occipital lobe (white arrow). (b) Diffuse lesions with linear/curvilinear enhancement along the bilateral cerebellar sulci (white arrows). (c) A focal lesion with nodular enhancement in the right occipital lobe (white arrow)

TABLE 2 Distributions of LM lesions in neuroimaging

	Cerebellum	Occipital lobe	Temporal lobe	Frontal lobe	Parietal lobe	Periventricular	Pons	Spinal cord	Cauda equine
MRI positive group, initial MRI ($N = 30$)	22 (73.33%)	13 (43.33%)	12 (40.00%)	9 (30.00%)	7 (23.33%)	1 (3.33%)	1 (3.33%)	0 (0.00%)	1 (3.33%)
Subgroup A, follow-up MRI ($N = 16$)	10 (33.33%)	10 (33.33%)	6 (20.00%)	6 (20.00%)	5 (16.67%)	0 (0.00%)	0 (0.00%)	2 (6.67%)	1 (3.33%)

Abbreviations: LM, leptomeningeal metastasis; MRI, magnetic resonance imaging.

All 86 patients with documented neurological signs and symptoms were considered valid. Symptom clusters resulting from elevated ICP were common, including headache (62/86), nausea (56/86), vomiting (55/86), and dizziness (55/86). The presence of one or more of the aforementioned symptoms reached 87.2% (75/86), which was the main reason for initiating the LM work-up. Other neurological symptoms were calculated in isolated LM patients to rule out the potential symptoms caused by concurrent brain/spine metastasis, including confusion (7/32), blurred vision (6/32), limb weakness (6/32), seizure (4/32), and cognitive impairment (4/32).

Characteristics of neuroimaging findings

A prompt head contrast MRI was initiated in all 86 patients with suggestive signs and symptoms of LM. Contrast spine MRI was performed at the physicians' discretion in 12 patients. Initial contrast MRI identified 30 patients with contrast-enhanced leptomeninges, constituting the MRI positive group. Patients with negative initial MRI findings were classified into the MRI negative group (Figure S3). Since follow-up neuroimaging of 16 patients from the MRI negative group was positive, these patients were defined as subgroup A (Figure S3). The neuroimaging characteristics of subgroup A were also investigated (Table 1). Figure 1 illustrates the different patterns of LM lesions as described in Table 1. Brain leptomeningeal metastases were found in 29 and 13 patients in the initial MRI positive group and subgroup A, respectively, accounting for the majority of cases of LM. Spinal leptomeningeal metastases and nerve root involvement were identified in four and three patients, respectively (Table 1). LM enhancement with a linear/curvilinear pattern was found in 26 out of 30 patients in the MRI positive group and in all 16 patients in subgroup A. A merely nodular pattern could only be seen in four out of thirty patients in the MRI positive group. Coexistence of a nodular pattern and linear/curvilinear pattern was found in ten and seven patients from the MRI positive and MRI negative groups, respectively. LM lesions were more diffuse rather than focal in the initial imaging of the MRI positive group (presented in 26 patients vs. 4 patients) and subgroup A (presented in 12 patients vs. 4 patients).

It was difficult to distinguish communicating hydrocephalus from obstructive hydrocephalus because of frequent effacement of the sulci and basal cisterns by the tumor. Concurrent hydrocephalus was significantly more common in the MRI positive group than in the MRI negative group (16/30 vs. 14/56, Chi-squared test, $p = 0.009$). Because follow-up imaging identified more hydrocephalus in the MRI negative group, the aforementioned significance no longer existed between the initial imaging of the MRI positive group and follow-up imaging of subgroup A (16/30 vs. 6/16, Chi-squared test, $p = 0.306$). More than half the patients had brain or spinal parenchymal metastasis in both the MRI positive and MRI negative groups (Table 1).

The distribution of the LM lesions were listed in Table 2. The surface of the cerebellum and occipital lobe was most frequently involved in both the initial imaging of the MRI positive group and subgroup A, followed by the temporal, frontal, and parietal lobes. Involvement of the surface of the spinal cord, pons, cauda equina, and periventricular was relatively rare.

Characteristics of CSF findings

Diagnostic CSF samples for all patients were obtained by prompt lumbar puncture. Cytology tests revealed tumor cells in the CSF of all 86 patients, confirming the diagnosis

TABLE 3 Baseline comparison of characteristics between the MRI positive and MRI negative groups

	Sex		Age		Smoking habit		Driver gene status		Intracranial pressure		CNS parenchymal metastasis		Hydrocephalus	
	Male	Female	≥65	<65	Smoker	Non-smoker	Mutations	Wild-type or NA	Elevated	Not elevated	Present	Absent	Present	Absent
All patients (N = 86)	38	48	18	68	26	60	73	13	52	34	52	34	30	56
MRI positive group (N = 30)	14	16	8	22	8	22	25	5	20	10	17	13	16	14
MRI negative group (N = 56)	24	32	10	46	18	38	48	8	32	24	35	21	14	42
p value		0.735		0.339		0.598		0.769		0.389		0.598		0.009*

Abbreviations: CNS, central nervous system; LM, leptomeningeal metastasis; MRI, magnetic resonance imaging; NA, not available.
*p < 0.05.

TABLE 4 Univariate and multivariate survival analyses

	Sex		Age		Smoking habbit		Driver gene status		Intracranial pressure		MRI		CNS parenchymal metastasis		Treatment							
	Male	Female	≥65	<65	Smo-ker	Nonsmoker	Wild-type or NA	Mutations	Elevated	Not elevated	Positive	Negative	Present	Absent	IT	Non IT	TKI	NonTKI	Chemo therapy	Non-chemo therapy	Radiation	Non-radiation
No. of patients	38	48	18	68	26	60	13	73	52	34	30	56	52	34	51	35	81	5	26	60	27	59
mOS/d	242	429	306	331	311	340	176	340	340	311	182	352	331	320	320	331	331	84	375	317	383	306
p value	0.006*		0.934		0.406		0.629		0.741		0.036*		0.725		0.898		0.335		0.332		0.315	
95%CI	61–423	283–575	8–604	298–364	75–547	256–424	59–293	304–376	302–378	127–495	10–354	257–447	280–382	197–443	218–422	189–473	290–372	0–228	174–576	221–413	318–448	152–460
HR	2.028										1.707											
p value	0.008*										0.044											
95% CI of HR	1.202–3.422										1.015–2.869											

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; IT, intrathecal; mOS, median overall survival; MRI, magnetic resonance imaging; NA, not available; TKI, tyrosine kinase inhibitor.
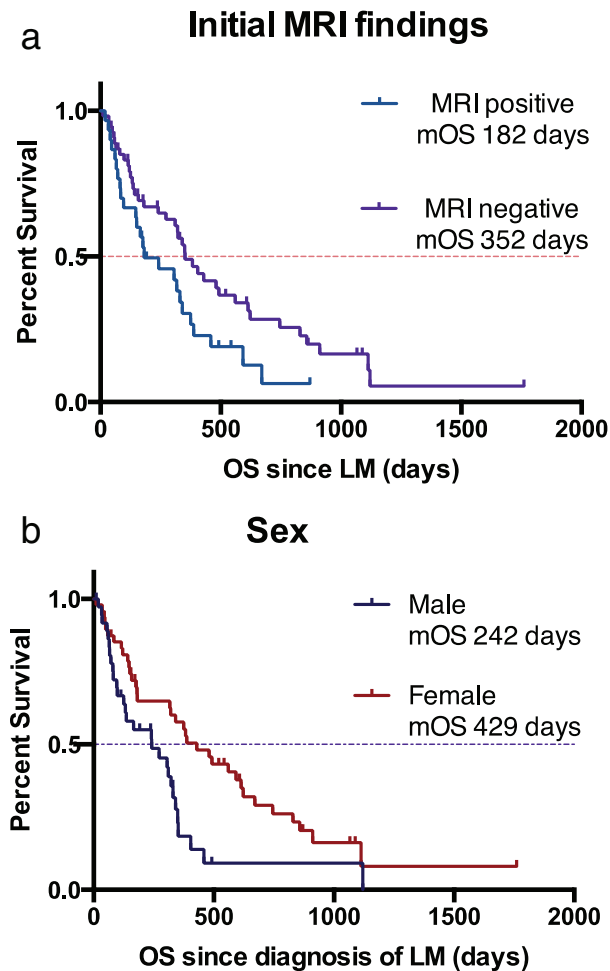Note:*p < 0.05.

FIGURE 2 Kaplan–Meier curve estimates for the binary independent factors; the + sign indicates censored data. (a) Whether LM enhancement emerged on the initial contrast MRI: MRI positive group versus MRI negative group. (b) Sex: male versus female. mOS, median overall survival; MRI, magnetic resonance imaging; OS, overall survival; LM, leptomeningeal metastasis

of leptomeningeal metastasis. The median and IQR between suggestive neurological signs/symptoms and cytological diagnosis of leptomeningeal metastasis for the MRI positive group and the MRI negative group were 32 (19.75–59.25) and 36 (21–66.25) days, respectively ($p = 0.954$ for medians, $p = 0.670$ for distribution). The median and IQR between initial MRI of neuroaxis and cytological diagnosis of leptomeningeal metastasis for the MRI positive group and the MRI negative group were 6(-1–13.5) and 11(1–31.75) days, respectively ($p = 0.602$ for medians, $p = 0.261$ for distribution). The majority of patients ($n = 52$, 60.5%) had an elevated ICP. The median ICP was 240 (range, 70–450) mm H_2O.

Baseline comparison between MRI positive and MRI negative groups

Patients with positive and negative contrast-enhanced MRI findings shared similar features ($p > 0.05$) in terms of

demographics, genetic alterations, ICP, and central nervous system (CNS) parenchymal metastases; however, the ratio of the complicated presence of hydrocephalus was significantly higher in the MRI positive group ($p = 0.009$, Table 3).

Treatment and survival analysis

Accompanied by the clinical applications of new generations of tyrosine kinase inhibitors (TKIs) during the seven-year period of this study, 81 patients received TKIs. Among them, 14 patients were treated with gefitinib, 10 with icotinib, 39 with erlotinib, 30 with osimertinib, 4 with crizotinib, 1 with alectinib, and 3 with brigatinib. Treatment strategies also included systemic treatments such as systemic chemotherapy ($n = 26$) and antiangiogenesis ($n = 4$), as well as focal therapy such as radiation therapy ($n = 27$) and intrathecal chemotherapy ($n = 51$). Ommaya reservoir placement ($n = 1$) and ventriculoperitoneal (VP) shunt ($n = 5$) were also noted to relieve the elevated ICP.

Among patients in the MRI positive and MRI negative groups, two and ten patients were lost to follow-up, while three and seven patients were still alive, respectively. OS data of patients were compared between binary statuses of the factors listed in Table 3, as well as characteristics of MRI findings and treatment. Since collinearity existed between the characteristics of hydrocephalus and LM enhancement features in the MRI findings ($p = 0.009$), the factor of hydrocephalus was excluded from the survival analysis. The remaining factors, including sex, age, smoking habit, driver gene status, ICP, CNS parenchymal metastases, initial LM enhancement findings, intrathecal chemotherapy, TKI administration, systemic chemotherapy, and brain radiation therapy, were considered independent factors and were analysed using the Kaplan–Meier curves (survival data are listed in Table 4). Compared with the log-rank test, different sex and LM enhancement findings on initial MRI led to significantly different OS ($p = 0.006$ and 0.036, respectively). Female patients with no LM enhancement on initial contrast MRI were shown to have prolonged survival (Figure 2).

Multivariate analysis was conducted among the aforementioned independent factors using Cox regression analysis with stepwise regression. The factors of LM enhancement on the initial contrast MRI and sex were both statistically significant prognostic factors (Table 4). The estimated hazard ratio (HR) of the presence of leptomeningeal enhancement on the initial contrast MRI was 1.707 ($p = 0.044$, 95% confidence interval of the HR 1.015–2.869). Similarly, males are estimated to have approximately a two-fold higher risk of death than females.

DISCUSSION

Neuroimaging has long been recognized as the most useful diagnostic tool for the diagnosis of LM. Its prognostic value has been explored in several studies during the past two

decades, but most could not draw this conclusion with statistical significance. Waki et al.[19] reviewed a series of patients with LM derived from solid tumours (lung, breast, gastric and other cancer types) between 1997 and 2005 and found seemingly inferior OS in MRI or CT-confirmed patients with LM compared with those without neuroimaging findings (median OS 45 vs. 67 days, respectively; $p = 0.09$). Ko et al.[20] focused on 283 patients with LM from lung adenocarcinoma between 2002 and 2016. The difference in median OS between patients with positive and negative neuroimaging findings was not statistically significant (median OS 3.48 vs. 4.31 months, respectively, $p = 0.711$). It was not until recent data[14] supporting the first EANO-ESMO guideline on LM was published that imaging was regarded as a predictor of patient outcomes. Neuroimaging may have begun to demonstrate prognostic value as a result of ongoing improvement in the survival of patients with LM from lung cancer with the development and application of new agents with potential benefits for LM in the modern era.[21] New-generation TKIs that have a potent ability to cross the blood–brain barrier benefit the population with genetic mutations, which is the majority of patients with LM.[16] Pemetrexed, bevacizumab, and other drugs[22,23] have also demonstrated benefits to patients with LM. An updated median OS of 182 and 352 days in patients with LM from lung adenocarcinoma in the MRI positive and MRI negative groups, respectively, provides insight into improved outcomes with contemporary therapies.

To the best of our knowledge, this is the first study in which initial MRI findings were found to be a prognostic factor in patients with LM from lung adenocarcinoma, emphasizing the importance of contrast MRI in the whole-process management of LM patients with lung adenocarcinoma. To make it more convincing and homogenous, we chose to use a cohort consisting of only the patients with cytologically confirmed LM and uniformly defined the overall survival from the date of confirmed cytological diagnosis of LM to the date of death. Meanwhile we demonstrated the possible delay of cytological diagnosis of LM were under control. With comparable demographic, genetic status, ICP, and treatment distributions, the median OS of patients in the MRI negative group was almost doubled compared with that of the MRI positive group. Cox regression established initial MRI findings as a prognostic factor for patients with LM. Although this result is to some extent understandable, knowing the prognostic difference between patients with positive and negative initial MRI findings helped to set reasonable expectations and make a treatment plan. As to why MRI positive patients had a shorter OS, we assumed that a larger tumor burden might be an important reason. Although LM lesions are difficult to quantify, the visibility of leptomeningeal enhancement is likely to represent a larger tumor burden compared with invisible lesions on contrast-enhanced MRI.

Interestingly, MRI findings in 16 patients in the MRI negative group (defined as subgroup A in Figure S3) turned positive in follow-up imaging studies. We further investigated the OS of this subgroup compared with that of the initial MRI positive

group. The Kaplan–Meier curve estimated the survival of subgroup A to be 382 days compared with 182 days for the MRI positive group. The log-rank test revealed a p-alue of 0.058, leading us to believe that the outcomes of patients with initial positive MRI findings were different from those with positive MRI findings in their follow-up studies. However, if we calculated OS since their MRI findings first appeared positive, there would be no significant difference in median OS between the MRI positive group and subgroup A (185 days vs. 276 days, $p = 0.124$). The appearance of positive findings on contrast-enhanced MRI might be regarded as a time point marking a very late stage in a patient's life journey, although further validation is warranted for this preliminary speculation.

Since positive findings in contrast-enhanced MRI are not sensitive enough for prompt diagnosis and intervention of LM, our study also suggested that the presence of leptomeningeal enhancement and hydrocephalus on contrast MRI were significantly correlated, indicating that hydrocephalus might be a surrogate marker for early identification of LM. Furthermore, novel neuroimaging techniques with higher sensitivity should be developed. In addition to the conventional CSF cytology test, EANO-ESMO guidelines also recommend promising approaches such as circulating tumour cells and genomic alterations in CSF,[24] although the specificity of the latter needs further validation.

It is widely acknowledged that the goal of treatment for patients with LM is to prolong survival and prevent neurological deterioration. Prompt diagnosis is essential for early intervention. In patients without positive MRI findings of the neuroaxis, clinical presentation is the only indication to initiate CSF cytology examinations in clinical practice. Thus, oncologists should have a strong awareness of suggestive symptoms of LM so as to identify and manage LM at an earlier stage in order to achieve an improved prognosis for these patients.

Our study has some limitations. First, because this was a retrospective cohort study, not all patients were investigated using contrast spine MRI, resulting in incomplete evaluation of the spinal cord and existing nerve roots. Second, we enrolled patients within a time period of 7.5 years, during which time successive new generations of TKIs and other systemic therapies began to be applied in clinical practice. However, not all patients had the opportunity to receive the newest generations of TKIs with better CNS penetration. Third, neuroimaging findings could not be further stratified, for instance, by patterns and/or severity, because of the sample size. Prospective studies with larger sample sizes are needed to verify our conclusions in the near future (data accumulation or multicentric cooperation). Finally, studies relating the imaging features to the biological behaviour of LM are warranted for a better understanding of the clinical course of LM and its management.

In conclusion, the prognosis of patients diagnosed with LM from lung adenocarcinoma is significantly different between patients with and without leptomeningeal enhancement in initial contrast-enhanced MRI under the premise of comparable baseline characteristics. Univariate and

multivariate analyses established positive initial contrast-enhanced MRI findings of the neuroaxis as a prognostic factor for the outcome of LM from lung adenocarcinoma with contemporary survival data. This implicates the importance of contrast-enhanced MRI in estimating the prognosis of patients with LM in addition to its diagnostic value.

CONFLICT OF INTEREST
All authors have completed the ICMJE uniform disclosure form. The authors have no conflict of interest to declare.

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