

Brain Metastases of Non-Small Cell Lung Cancer: Magnetic Resonance Spectroscopy for Clinical Outcome Assessment in Patients with Stereotactic Radiotherapy

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Background: Brain metastases (BM) are severe incidents among patients with non-small cell lung cancer (NSCLC) and have been associated with significant morbidity and decreased survival; thus, new methods are required to improve clinical management. Magnetic resonance spectroscopy (MRS) allows noninvasive measurements of biochemical information from tumor tissue, providing clinically useful imaging biomarkers. The primary aim of this study was to explore the application of MRS in the assessment of tumor prognosis after stereotactic radiotherapy in NSCLC patients with BM.

Patients and Methods: MRS was performed on NSCLC patients attending Qingdao Center Hospital with suspected BM, and 68 patients were included in the survival analysis. The qualitative and quantitative parameters of MRS metabolites, such as choline (Cho), creatine (Cr), and N-acetyl-aspartate (NAA), were recorded. To select a cutoff for MRS metabolite parameters in the tumor and to distinguish patients who had recurrence, we performed an ROC curve analysis. Univariate and multivariate Cox regression analyses were used to assess the association between MRS metabolite parameters and clinical cancer prognosis.

Results: The average age was 56 years. A total of 68 NSCLC patients underwent metabolic evaluation with single voxel proton MRS and were selected for retrospective analysis. According to the area under the curve (AUC) to predict recurrence, the MRS metabolite parameters were determined as Cho (AUC=0.550), Cr (AUC=0.415), NAA (AUC=0.524), NAA/Cr (AUC=0.600), Cho/Cr (AUC=0.723), and Cho/NAA (AUC=0.543). Cho and Cr predicted poor survival while Cho/Cr and NAA/Cr predicted improved survival ($P<0.05$). In the multivariate model with adjustment to establish the potential role of MRS metabolite parameters, Cho/Cr showed a significant association with OS ($P=0.009$) and PFS ($P=0.006$) after stereotactic radiotherapy.

Conclusion: The positive results of this study indicate the predictive value of metabolic characteristics of BM detected with MRS for the outcome after stereotactic radiotherapy.

Keywords: brain metastases, magnetic resonance spectroscopy, stereotactic radiotherapy

Introduction

Lung cancer is the most common cause of death from malignant tumors worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 80%-85% of all lung cancer cases.^{1,2} Brain metastases (BM) are a frequent neurological complication of NSCLC and have historically been associated with a poorer prognosis.

BM are estimated to occur in approximately 30–54% of patients with NSCLC after treatment.^{3,4} As shown in a recent multicenter clinical study on a group of patients with NSCLC with BM, the median survival time was 7 months with the best supportive care.^{5–8} Surgical resection and radiotherapy are the current local methods utilized in the treatment of BM in NSCLC, but evidence on how to utilize these local methods precisely is lacking. The lack of a consistent and reliable prognostic marker has prompted us to look for a better tool.

Molecular tests of metabolic processes in tumor tissue have provided new prognostic markers, which are starting to be incorporated into clinical management strategies.^{9,10} Novel noninvasive biochemical biomarkers of tumor prognosis would improve tumor characterization and would have the advantage of being available for cases where radiotherapy was not performed. The utility of advanced magnetic resonance imaging (MRI) techniques in diagnosis and evaluation of treatment response has been validated.¹¹ This study explores to what extent magnetic resonance spectroscopy (MRS) can play a role in NSCLC patients with BM and analyzes clinical studies with particular reference to prognostic value.

Since the 1980s, MRS has been applied clinically for the examination of tumor metabolic processes,¹² and this area of research continues to provide new insights into tumors.^{13,14} Clinical MRS enables the noninvasive evaluation of the biochemical composition of tumor tissues, which is used to examine metabolic alterations in cancers and measures the concentration of variety of biomolecules from a volume of interest.¹⁵ MRS is widely used to study the biology of tumor metabolism and has also been shown to effectively estimate treatment efficacy in tumors.^{16–18} Therefore, it is possible to investigate the metabolic features of BM that can be predictive for patient survival. However, thus far, no previous study has investigated MRS metabolite parameters for their prognostic potential significance in NSCLC with BM. Taking into account the characteristics of tumor metabolism, MRS may further improve outcome prediction. This information would be valuable to further identify high-risk patients for close surveillance and provide clinical benefit by identifying nonresponding patients for alternate therapy. In this study, we aimed to evaluate the predictive roles of MRS metabolite parameters as an imaging predictor of survival in NSCLC patients with BM.

Methods

Patient Selection and Study Design

We reviewed a total of 68 NSCLC patients with BM at Qingdao Center Hospital between March 2015 and September 2017. The patient flow chart is shown in Figure 1. BM were detected by enhanced MRI. Extracranial disease had been resected or stably controlled, and all patients had ≤ 3 BM. All NSCLC patients with BM signed a consent form to undergo MRS. MRI and MRS imaging were performed before treatment. The patient selection criteria were as follows: (i) surgery, percutaneous lung puncture biopsy or bronchoscopic biopsy pathological diagnosis of NSCLC; (ii) no contraindications to MRI; (iii) all initial Eastern Cooperative Oncology Group (ECOG) scores were ≤ 2 ; (iv) no neurosurgery, stroke, history of primary brain tumor; and (v) no other medical pathologies of the nervous system. Patient characteristics, including gender, age, ECOG score, smoking status, histology, primary T stage, primary N stage, primary AJCC stage, and MRS metabolic parameters were collected from electronic medical records. This retrospective cohort study was approved by the institutional review board of Qingdao Center Hospital institutions. All patients were provided with written informed consent. The study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki.

¹H-MRS Metabolic Characteristics of BM

All patients underwent MRI (T1, T2-weighted and dynamic contrast-enhanced images) and single-voxel ¹H-MRS using 3.0 T clinical scanner magnetic resonance machine (Philips Healthcare, Andover, MA, USA) prior to treatment. The point-resolved spectroscopic (PRESS) method was used for multivoxel MRS sequence scanning (TR:2000 ms, TE:144 ms, FOV: 230 mm \times 230 mm, slice thickness: 10 mm, scan time: 350 seconds, voxel size: 1 \times 1 \times 1mm³). The multivoxel MRS imaging was acquired in two different tissues: tumor tissue and normal tissue, and avoids influencing factors the scalp, such as necrosis, skull, bleeding, and blood vessels. The scan program performed water suppression scanning and voxel shimming. (Figure 2) A commercially available imaging workstation was used for postprocessing of ¹H-MRS metabolite data. The MRI and ¹H-MRS of patients were interpreted by two experienced radiologists who were aware of the tumor location and draw the MRS regions of interest. The center

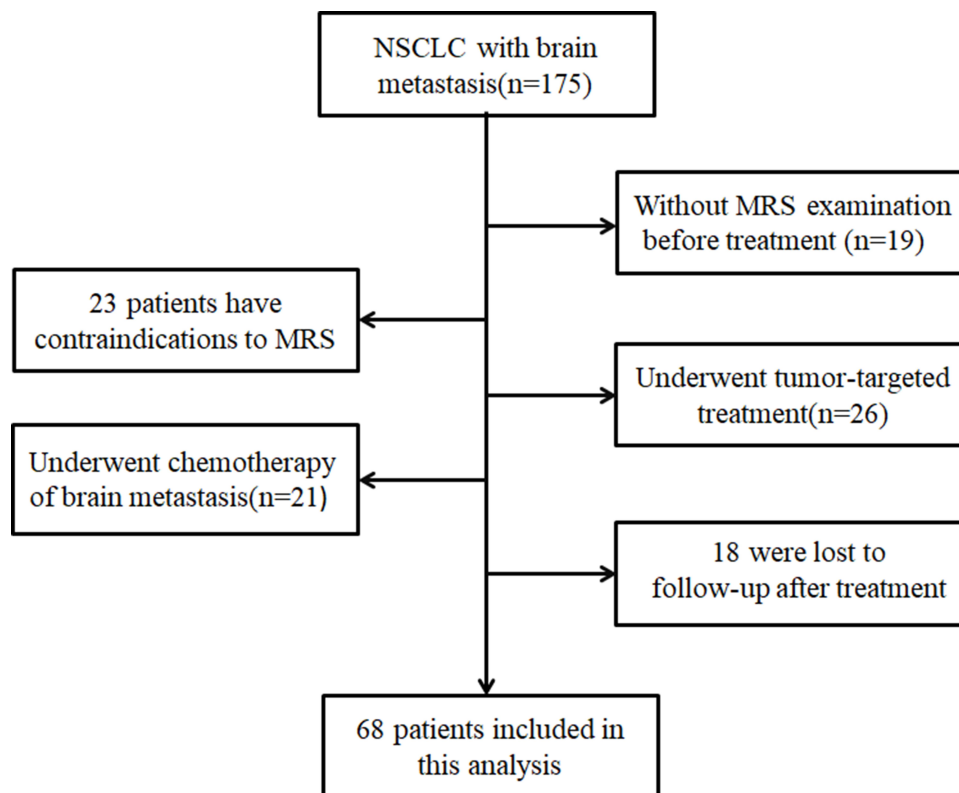


Figure 1 Flow diagram of the patient selection process.

of the voxel grid is located in the maximum area of the lesion cross-section. The relative metabolite intensities of the signals from choline (Cho), N-acetyl-aspartate (NAA), and creatine (Cr) in the tumor voxels were analyzed. The metabolite ratios examined included Cho/NAA, Cho/Cr, and NAA/Cr.

Response Evaluation and Follow-Up

Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.¹⁹ According to the RECIST guidelines, complete response (CR) was defined as total regression of all assessable lesions; partial response (PR) was defined as a decrease of at least 30% in the sum of the longest dimensions of the target lesions; progressive disease (PD) was defined as more than a 20% increase in primary tumor volume or appearance of new lesions; the remaining patients which did not meet the criteria of PD or PR were categorized as stable disease (SD). Follow-up protocol was performed at regular intervals: 3 monthly for the first 3 years, 6 monthly during the following year and annually thereafter. The MRI/MRS was performed during the follow-up and the patients received laboratory tests, physical

examination, computed tomography or PET-CT for evaluation of primary and distant metastasis. Besides, we performed the imaging examination at every follow-up. During the follow-up, all patients did not receive any systematic treatment. If the patients have recurrence or metastasis, we conducted local or systemic treatment. The endpoints overall survival (OS) and progression-free survival (PFS), were defined as the time from the start of radiotherapy to the date of death and tumor progression, respectively. Follow-up was conducted on 68 patients until November 2018. The median follow-up time was 16 months (range: 8–36 months).

Statistical Analysis

SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) was used in all statistical analyses. Associations of the tumor response to radiotherapy with ¹H-MRS-detected metabolic characteristics of BM were evaluated by the chi-square test with continuity correction. The sensitivity and specificity were calculated using a receiver operating characteristic (ROC) analysis. To test our research hypothesis, univariate Cox regression was performed on the data of each individual measured metabolite. Categorical variables with

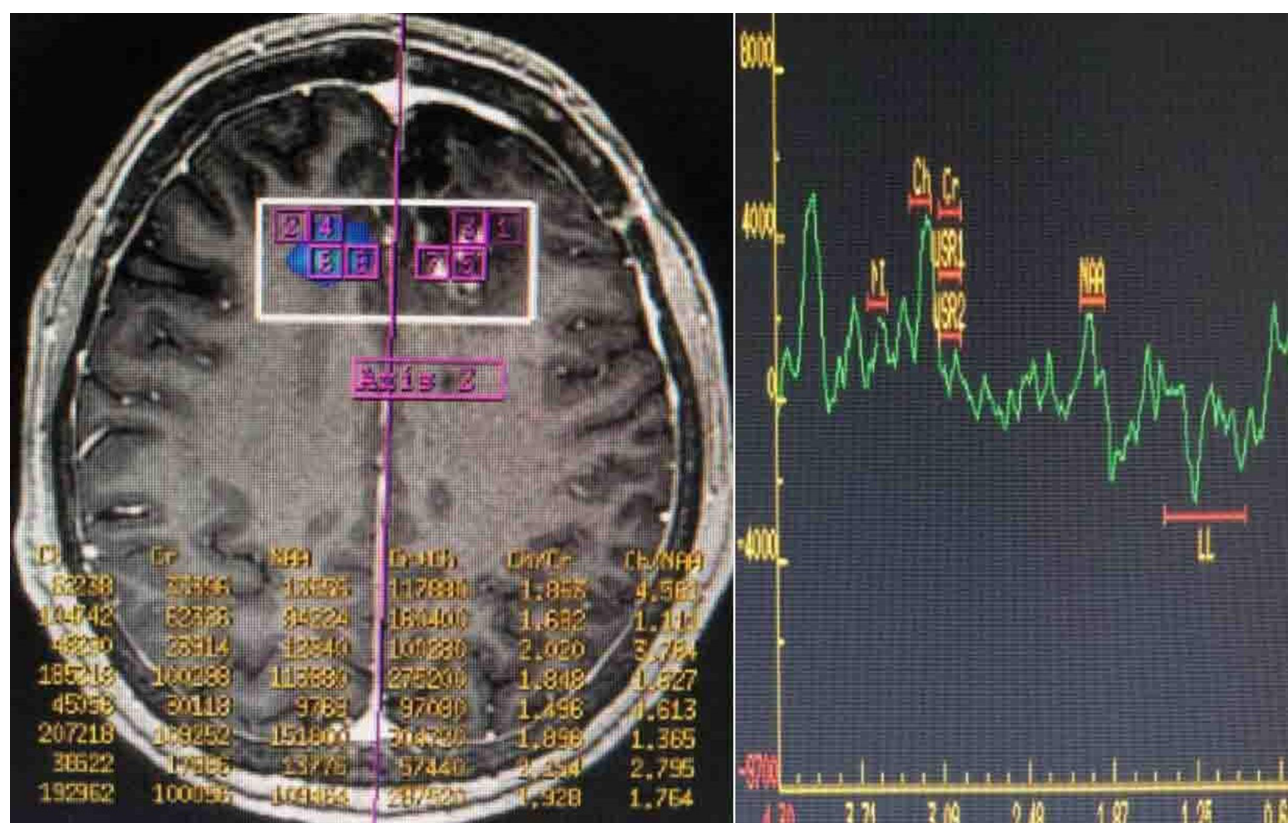


Figure 2 Data acquired at 3.0 T with short echo time elliptical excitation chemical shift imaging.

$P < 0.05$ in univariate Cox regression analysis were included in a multivariate Cox regression model. Differences were considered significant when $P < 0.05$; all P values presented are two-sided.

Results

Patient Characteristics

Table 1 presents the clinical characteristics of 68 enrolled patients, 34 women (50%) and 34 men (50%), and all received stereotactic radiotherapy (48–60Gy/6–8 fraction, median: 8Gy). The average age of patients in this study was 56 years (range, 48–71 years). In the majority of patients, the histological type of NSCLC was adenocarcinoma. A total of 36 (52.9%) patients had a prior history of smoking. There were 29 patients of intracranial progression, 57 patients with any progression, 55 deaths at the time of the final follow-up. The median survival time of the included patients was 19.5 months.

Analysis of ^1H -MRS Metabolites

The patients had a median Cho of 2.05 (range, 0.93–3.90), NAA of 0.78 (range, 0.23–1.71), Cr of 1.27 (range,

0.45–2.10), Cho/Cr of 1.65 (range, 0.72–5.55), Cho/NAA of 2.48 (range, 0.88–13.13) and NAA/Cr of 0.63 (range, 0.18–1.91). All of the parameters that are calculated from ^1H -MRS are summarized in Table 2. We attempted to establish the optimal cutoff value for ^1H -MRS metabolite parameters in our study population through ROC curve analysis. Cho/Cr was found to have the largest area under the curve (AUC=0.723; 95% confidence interval [CI], 0.594–0.851; $P=0.002$). (Figure 3) The AUCs were 0.524 ($P=0.739$), 0.550 ($P=0.481$), 0.415 ($P=0.233$), 0.543 ($P=0.545$) and 0.600 ($P=0.159$) for NAA, Cho, Cr, Cho/NAA and NAA/Cr, respectively. The optimal cutoff value for the NAA, Cho, Cr, Cho/NAA, Cho/Cr and NAA/Cr were 0.50, 1.50, 0.50, 3.61, 1.46 and 0.99, respectively. Based on the ^1H -MRS metabolite parameter cutoff values, the patients were stratified into two groups.

Prognostic Value of ^1H -MRS Metabolite Parameters and Clinicopathological Factors

The results of the univariate analyses of clinicopathological factors are included in Table 3. Univariate analysis

Table 1 Baseline Clinical Characteristics of 68 Patients with BM from NSCLC

Factors	No. of Patients (%)
Age (years)	
<60	31(45.6)
≥60	37(54.4)
Gender	
Male	34(50.0)
Female	34(50.0)
ECOG score	
0–I	40(58.8)
2	28(41.2)
Smoking status	
Yes	36(52.9)
No	32(47.1)
Histology	
SCC	20(29.4)
AD	48(70.6)
Primary T stage	
T1	18(26.5)
T2	20(29.4)
T3	14(20.6)
T4	16(23.5)
Primary N stage	
N1	14(20.6)
N2	20(29.4)
N3	19(27.9)
N4	15(22.1)
Primary stage	
I	17(25.0)
II	26(38.2)
III	25(36.8)
No. of BM	
1	30(44.1)
2	18(26.5)
3	20(29.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; AD, adenocarcinoma; BM, brain metastases.

demonstrated that age (HR, 2.182; 95% CI, 1.067–4.460; $P=0.032$) is correlated with OS, and we found no significant association between OS and clinicopathological characteristics, including gender, primary T stage, primary N stage, primary stage, histology, ECOG score, and smoking status (all $P>0.05$). Age (HR, 2.530; 95% CI, 1.221–5.242; $P=0.013$) and ECOG score (HR, 2.140; 95% CI, 1.103–4.155; $P=0.025$) were significantly associated with PFS (Figure 4). Table 4 shows the findings from univariate analyses of the $^1\text{H-MRS}$

Table 2 $^1\text{H-MRS}$ -Detected Metabolic Characteristics of Brain Metastases for NSCLC Patients

Metabolic Characteristics	All Patients, Median (Range)
Cho	2.05(0.93–3.90)
Cr	1.27(0.45–2.10)
NAA	0.78(0.23–1.71)
Cho/Cr	1.65(0.72–5.55)
NAA/Cr	0.63 (0.18–1.91)
Cho/NAA	2.48(0.88–13.13)

Abbreviations: Cho, choline; Cr, creatine; NAA, N-acetyl-aspartate.

metabolite parameters. In the univariate analyses, Cho/Cr (HR, 3.424; 95% CI, 1.578–7.432; $P=0.002$) predicted OS, and Cho/Cr (HR, 5.167; 95% CI, 1.997–13.364; $P=0.001$) and NAA/Cr (HR, 2.686; 95% CI, 1.341–5.380; $P=0.005$) predicted PFS. We did not find significant correlations between OS and the following metabolite parameters: Cho, Cr, NAA, NAA/Cr, and Cho/NAA (all $P>0.05$).

Multivariate Analysis of Independent Prognostic Indicators

As shown in Table 5, age, ECOG score, NAA/Cr and Cho/Cr were included in the multivariate analyses. The results showed that Cho/Cr was significantly related to OS (HR, 2.956; 95% CI, 1.315–6.645; $P=0.009$) and PFS (HR, 3.925; 95% CI, 1.489–10.348; $P=0.006$). Age could not be a prognostic factor for OS ($P=0.235$) and PFS ($P=0.135$). Therefore, multivariate analysis demonstrated that Cho/Cr is considered an independent prognostic indicator for OS and PFS.

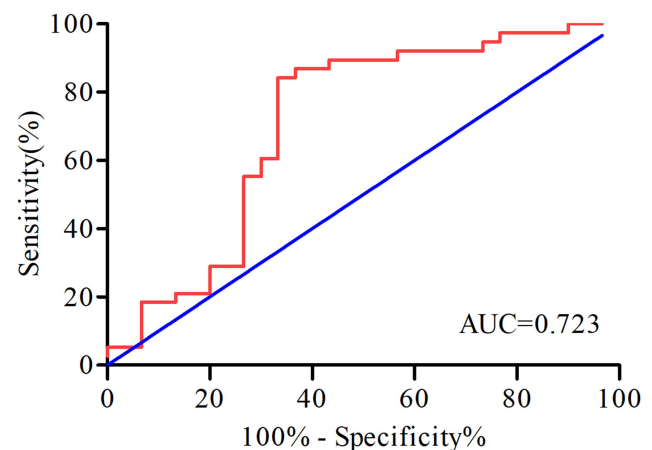
**Figure 3** ROC curve of Cho/Cr for recurrence prediction.

Table 3 A Summary of the Univariate Cox Regression Model Based on Baseline Characteristics

Factors	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<60	Reference			Reference		
≥60	2.182	1.067–4.460	0.032	2.530	1.221–5.242	0.013
Gender						
Male	Reference			Reference		
Female	0.651	0.325–1.305	0.227	1.224	0.641–2.337	0.541
ECOG score						
0–1	Reference			Reference		
2	1.182	0.611–2.286	0.620	2.140	1.103–4.155	0.025
Smoking status						
No	Reference			Reference		
Yes	0.902	0.468–1.740	0.759	1.015	0.530–1.942	0.965
Histology						
SCC	Reference			Reference		
AD	0.769	0.389–1.523	0.452	1.364	0.642–2.896	0.419
Primary T stage						
T1–T2	Reference			Reference		
T3–T4	1.176	0.604–2.290	0.633	1.154	0.604–2.204	0.665
Primary N stage						
N1–N2	Reference			Reference		
N3–N4	1.090	0.552–2.155	0.804	0.872	0.455–1.668	0.678
Primary stage						
I	Reference			Reference		
II–III	0.535	0.254–1.126	0.100	1.158	0.540–2.482	0.707
No. of BM						
I	Reference			Reference		
2–3	1.426	0.694–2.928	0.334	1.268	0.641–2.507	0.495

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; AD, adenocarcinoma; BM, brain metastases.

Discussion

Metabolic alterations of tumor tissues are associated with patient prognosis. The analysis of metabolic feature composition can offer an early approach to assess the association between metabolic parameter and outcomes. This study showed that the Cho/Cr levels of tumors, detected noninvasively by ¹H-MRS at diagnosis, predict survival in a cohort of NSCLC patients with BM, and Cho/Cr was validated as the only independent factor for OS and PFS in the multivariate analysis. Gender, primary T stage, primary N stage, primary stage, histology, ECOG score, and smoking status had no significant effect on survival.

Metabolic alterations are one of the core features of tumor cells and are considered to be an important indicator

of tumor diagnosis and evaluation of tumor biological behavior. In tumors, metabolites can be monitored before treatment by MRS, and MRS shows great promise as an imaging technique for identifying benign and malignant tumors in the brain.^{20,21} In recent years, studies have reported that MRS metabolic parameters can reflect the biochemical composition of brain tumors and can provide valuable prognostic information in gliomas. More comprehensive descriptions of the molecular basis for the known biochemical changes in metabolites in tumors are available. The typical MRS-detected metabolic profile of brain metastases includes reduction in Cr and NAA, an increase in Cho and appearance of Lip peaks.^{16,22,23} Cho reflects the turnover of the cell membrane during normal cell

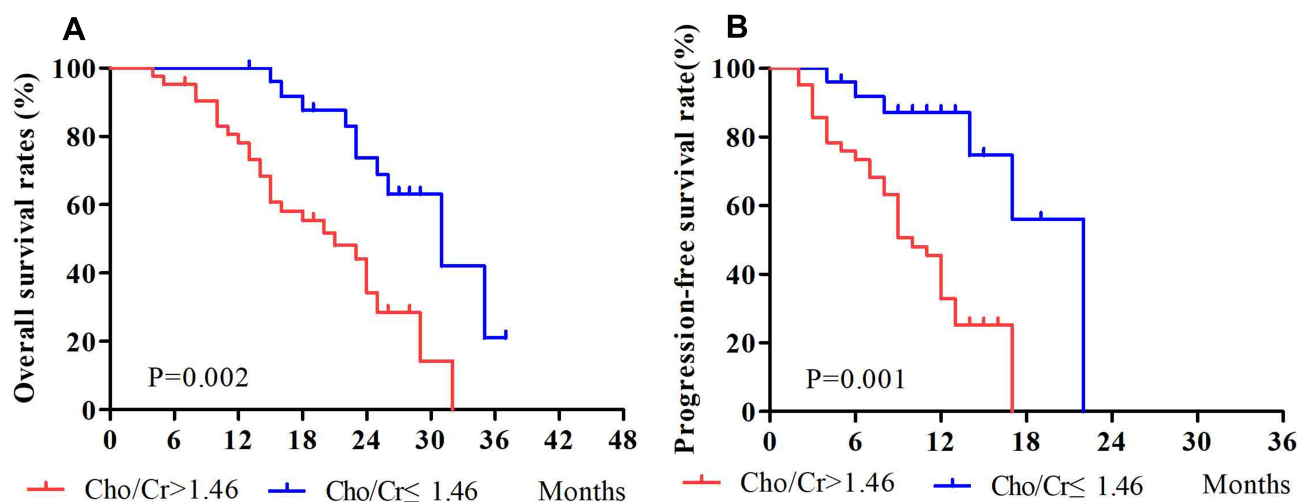


Figure 4 Survival curves for overall survival (A) and progression-free survival (B) in Cho/Cr \leq 1.46 and Cho/Cr $>$ 1.46 group in non-small cell lung cancer patients with brain metastases.

proliferation.^{24,25} A greater decrease in Cho may be related to less tumor proliferation, and thus better prognosis.²⁶ The findings of Maheshwari et al²⁴ prove that the Cho signal detected by MRS is strongly correlated with phosphocholine and free Cho, while phosphatidylcholine in intact cell membranes is not. Therefore, we

speculate that the Cho biological signal may reflect cell proliferation and cell death. Therefore, a smaller decrease in Cho may actually reflect an increase in tumor cell death, which could account for the improved clinical outcomes. In a study by Tedeschi et al,²⁷ all progressive cases showed a Cho signal increase between studies of more

Table 4 A Summary of the Univariate Cox Regression Model Based on ¹H-MRS Parameters

Factors	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Cho ≤1.50 >1.50	Reference 1.753	 0.397–7.743	 0.459	Reference 3.175	 0.120–4.935	 0.242
Cr ≤0.50 >0.50	Reference 0.600	 0.142–2.538	 0.488	Reference 0.669	 0.160	 2.799
NAA ≤0.50 >0.50	Reference 0.935	 0.401–2.179	 0.876	Reference 1.104	 0.520–2.343	 0.798
Cho/Cr ≤1.46 >1.46	Reference 3.424	 1.578–7.432	 0.002	Reference 5.167	 1.997–13.364	 0.001
NAA/Cr ≤0.99 >0.99	Reference 1.904	 0.927–3.912	 0.080	Reference 2.686	 1.341–5.380	 0.005
Cho/NAA ≤3.61 >3.61	Reference 1.475	 0.741–2.934	 0.268	Reference 1.137	 0.588–2.197	 0.703

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; Cho, choline; Cr, creatine; NAA, N-acetyl-aspartate.

Table 5 Multivariate Analysis of OS and PFS in 68 NSCLC Patients with BM

Variables	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<60	Reference			Reference		
≥60	1.574	0.744–3.327	0.235	1.774	0.836–3.763	0.135
ECOG score						
0–1				Reference		
2				1.596	0.812–3.137	0.175
Cho/Cr						
≤1.46	Reference			Reference		
>1.46	2.956	1.315–6.645	0.009	3.925	1.489–10.348	0.006
NAA/Cr						
≤0.99				Reference		
>0.99				1.741	0.849–3.571	0.130

Abbreviations: BM, brain metastases; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; Cho, choline; Cr, creatine; NAA, N-acetyl-aspartate.

than 45%, whereas all stable cases showed an elevation of less than 35%, no change, or even a decreased signal. Wald et al²⁸ found that a reduction in Cho levels indicates the transformation of tumors to necrotic tissue by MRS imaging. Menard et al²⁹ conducted a histopathologic study of diagnostic validity to evaluate the value of Cho levels in a malignant prostate gland, and the results confirmed that Cho levels were correlated with tumor recurrence. In a study of malignant breast tumors, Mackinnon et al³⁰ found that the Cho peak detected by MRS could distinguish between benign and malignant breast tumors with relatively high sensitivity and specificity. However, our results demonstrated that the Cho levels of BM are not an independent prognostic factor ($P=0.459$ for OS and $P=0.242$ for PFS). These discrepancies may reflect the heterogeneity of patients in each clinical study.

In addition to the Cho results, another important finding is that patients with higher Cho/Cr had worse prognosis, which is consistent with the expected high rates of proliferation in aggressive tumors. Matsusue et al³¹ revealed that Cho/Cr ($P<0.01$) has the potential to improve the overall diagnostic accuracy in distinguishing glioma progression. Fink et al³² found that Cho/Cr (AUC=0.913, $P=0.002$) appear to outperform DWI for distinguishing glioma recurrence. A study of eighty-five cancer patients with brain metastases demonstrated that a decrease in the Cho/Cr ratio likely reflects an inhibition of proliferative activity and early apoptotic cell death ($P<0.001$).³³ Despite the positive trends observed, recent work of Liu et al³⁴ showed that Cho/Cr >2 is not

significantly correlated with mortality from brain metastases in lung cancer patients after radiotherapy. Can MRS accurately evaluate survival and tumor progression after radiotherapy for BM in NSCLC patients? The results of the Kaplan-Meier analysis and Log rank test of our study revealed that patients with elevated Cho/Cr values (Cho/Cr>1.46) exhibited a poorer prognosis than those with Cho/Cr≤1.46 (OS, $P=0.002$; PFS, $P=0.001$). In our work, multivariate analysis performed using the characteristics selected in the univariate analysis revealed that Cho/Cr was significantly correlated with mortality ($P=0.009$) and tumor progression ($P=0.006$). Combined with previous research, these data indicate that MRS metabolic parameters can play an important role in cancer prognosis.

Our research has several limitations, including the limited number of enrolled patients from a single-center retrospective study, which can be associated with inherent selectivity bias. In addition, although we used statistical methods accurately, the variable cutoff values of NAA, Cho, Cr, Cho/Cr, Cho/NAA and NAA/Cr are limitations to this study. Since the cutoff values in this and other previous studies analyzing MRS metabolic parameters are not consistent, another large-scale study or prospective study is required to confirm accurate cutoff values. Therefore, the results need to be further validated in larger cohorts and prospective studies.

After stereotactic radiotherapy for BM, the patients with elevated Cho/Cr values had poorer survival, but increased NAA, Cho, Cr, Cho/NAA and NAA/Cr did not serve as reliable indicators of BM progression.

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Disclosure

The authors report no conflicts of interest in this work.

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