Factors Linked to Prognosis in Patients with Leptomeningeal Metastasis Diagnosed by Spinal Magnetic Resonance Imaging

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Abstract:

Introduction: Leptomeningeal metastasis (LM) is known to demonstrate a very poor prognosis. The purpose of this study was to evaluate the prognostic factors in LM cases diagnosed by spinal magnetic resonance imaging (MRI).

Methods: We retrospectively analyzed 19 patients with LM detected by spinal MRI between 2010 and 2017.

Results: The primary tumors were breast carcinoma (n = 7), lung carcinoma (n = 6), lymphoma (n = 3), colorectal carcinoma (n = 2), and gastric carcinoma (n = 1). Thirteen patients exhibited preceding brain metastasis, and 11 of these exhibited metastasis in the posterior fossa. Ten patients exhibited limb paralysis. Performance status at diagnosis was 0-1 in 6 patients, 2 in 9 patients, and 3-4 in 4 patients. Testing of cerebrospinal fluid revealed malignant cells in 9 patients.

On MRI, 11 patients demonstrated disseminated tumor lesions at the cervical cord level, 15 patients at the thoracic cord level, and 11 patients below the conus level. Eleven patients received radiation therapy, while intrathecal chemotherapy was performed in 9 patients.

Univariate analysis revealed cervical cord level lesions, intrathecal chemotherapy, paralysis, and performance status as prognostic factors. Multivariate analysis identified existence of a cervical cord lesion as associated with a poor prognosis (hazards ratio (HR) 3.46, 95% confidence interval (CI) 1.12-12.2), while administration of intrathecal chemotherapy was associated with a good prognosis (HR 0.15, 95% CI 0.026-0.67).

Conclusions: In LM patients, cervical cord level lesions are a negative factor for prognosis, and performance of intrathecal chemotherapy is a positive factor for prognosis.

Keywords:

leptomeningeal metastasis, spinal MRI, intrathecal chemotherapy, cervical cord lesion, paralysis, performance status

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Introduction

Leptomeningeal metastasis (LM) is usually observed in patients with advanced-stage malignant tumors. LM is metastasis from various malignant tumors that spreads to the cerebrospinal fluid (CSF) and leptomeninges; it is clinically diagnosed in 4% to 15% of patients with solid tumors and 5% to 15% of patients with leukemia and lymphoma[1,2)]. The median survival of these patients has been reported to be 2-3 months[3-6)].

LM can cause almost any neurologic symptom and originates in different areas of the central nervous system, brain, cranial nerves, and spinal cord, because malignant cells can move to any location on the neurospinal axis[6)]. For this reason, some patients who exhibit symptoms such as sensory or motor disturbance in their limbs are suspected of spinal disease. In such cases, spinal magnetic resonance imaging (MRI) sometimes leads to a diagnosis of LM.

We conducted a retrospective evaluation of our experience with patients with LM who were diagnosed by spinal MRI, in order to analyze prognostic factors.

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Table 1. Patient Characteristics.

		N
Total		19
Male		9
Female		10
Age at diagnosis		57
Primary tumor	Breast	7
	Lung	6
	Lymphoma	3
	Colorectal	2
	Gastric	1
Performance status at diagnosis	0-1	6
	2	9
	3-4	4
Preceding brain metastasis (Posterior fossa)		13
		(11)
Symptoms at diagnosis	Sensory deficit	15
	Numbness in limbs	12
	Paralysis	10
	Pain	5
CSF testing	Malignant cells (+)	9
LM lesions on MRI	Cervical cord level	11
	Thoracic cord level	15
	Conus level	11
Treatment of LM	Radiation therapy	11
	Inthrathecal chemotherapy	9
	Systemic chemotherapy	1

CSF: cerebrospinal fluid
LM: leptomeningeal metastasis

Materials and Methods

Patients diagnosed between 2010 and 2017 as demonstrating meningeal dissemination of the spine on a gadolinium-enhanced MRI were included in this study. The diagnosis of LM was based on the reports of the radiologists in our center. The demographic data of these patients, as well as their clinical features and treatment modalities, were collected, and potential prognostic factors were evaluated.

For univariate analysis, survival rates were calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. The multivariate Cox proportional hazards model was used to determine the independent prognostic factors for survival. A P value < 0.05 was considered to show a significant difference on univariate and multivariate analysis.

Results

There were 19 patients diagnosed as demonstrating meningeal dissemination in the spine during the study period. Their characteristics are shown in Table 1. Their average age at diagnosis of LM was 57 years. The primary tumors were breast carcinoma (7 patients), lung carcinoma (6 patients), lymphoma (3 patients), colorectal carcinoma (2 patients), and gastric carcinoma (1 patient).

At the time of LM diagnosis, their performance status (PS) was 0-1 in 6 cases, 2 in 9 cases, and 3-4 in 4 cases. Thirteen patients (68%) exhibited preceding brain metastasis, and 11 of these demonstrated metastasis in the posterior fossa. Sensory deficit was observed in 15 patients (79%). A total of 12 patients felt numbness, and 10 patients exhibited paralysis in their limbs, while 5 patients felt pain in their limbs.

On CSF testing, malignant cells were detected in 9 patients (47%), and there were 3 patients (16%) that were required to be tested multiple times to prove positive.

MRI images of representative cases are shown in Fig. 1. 11 patients demonstrated disseminated tumor lesions at the cervical cord level, 15 patients at the thoracic cord level, and 11 patients below the conus level.

Fig. 2 shows the Kaplan-Meier survival curve after the diagnosis of LM in patients with cervical cord level lesions, compared with that in patients without cervical cord level lesions.

Eleven patients received radiation therapy for the treatment of LM. Intrathecal chemotherapy was performed in 9 patients, and systemic chemotherapy in 1 patient. Fig. 3 shows the Kaplan-Meier survival curve in patients who received intrathecal chemotherapy compared with that in patients who did not.

The median length of survival after the diagnosis of me-

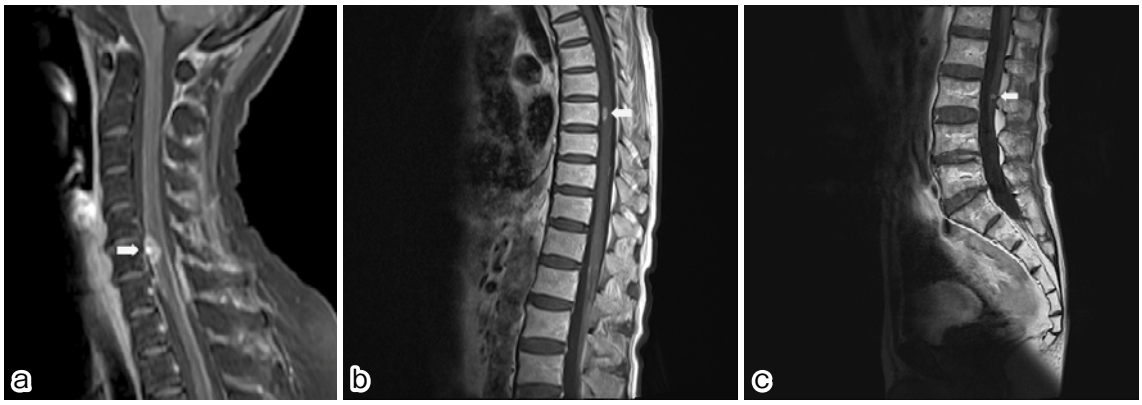

Figure 1. MRI imaging of the spinal cord.
(a) leptomeningeal dissemination at cervical cord level
(b) leptomeningeal dissemination at thoracic cord level
(c) leptomeningeal dissemination below conus level

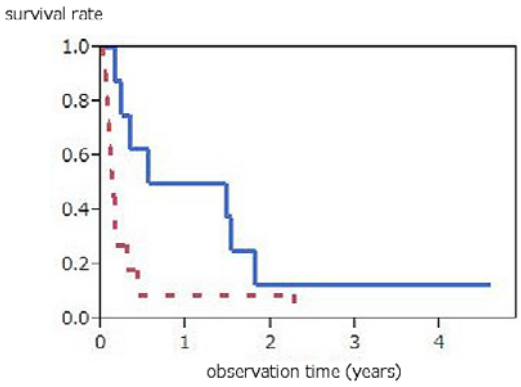

Figure 2. Kaplan-Meier analysis of survival related to cervical cord level lesions.
The dotted line indicates patients having cervical cord level lesions, and the solid line indicates patients without cervical cord level lesions.

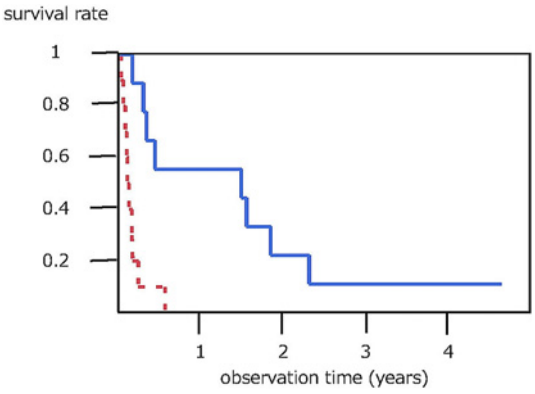

Figure 3. Kaplan-Meier analysis of survival related to intrathecal chemotherapy.
The dotted line indicates patients without intrathecal chemotherapy, and the solid line indicates patients without cervical cord level lesions.

tastasis was 59 days. On univariate analysis, the factors that were found to influence overall survival were demonstrating disseminated cervical lesions (P = 0.017), receiving intrathecal chemotherapy (P = 0.0005), exhibiting paralysis (P = 0.014), and PS (P = 0.011). Detailed results are presented in Table 2.

On multivariate analysis, existence of cervical cord level lesions exhibited a higher risk of death (hazard ratio (HR) 10.8, 95% confidence interval (CI) 2.4-79.4), while administration of intrathecal chemotherapy was identified as a factor associated with a good prognosis (HR 0.08, 95% CI 0.01-0.49) (Table 3).

Discussion

In this study, we examined the progress of patients diagnosed as exhibiting LM, which was detected by spinal MRI. Consistent with previous reports[7,8], this study indicated that breast cancer and lung cancer demonstrated a high probability of being the causes of LM, but we also studied cases caused by colorectal cancer and gastric cancer.

Knafo et al. reported that spinal LM should be suspected in patients with a known history of cancer presenting with back pain or radiculomedullary deficit[9]. In this study, 15 patients exhibited sensory deficit, 12 patients felt numbness in their limbs, and 10 patients exhibited paralysis at the time of diagnosis. If such symptoms occur, checking for LM may be necessary.

LM is usually diagnosed by combining CSF examination and gadolinium-enhanced MRI. Identification of malignant cells in the CSF on cytology is considered to be the gold standard for the diagnosis of LM[4]. Researchers reported that this test was estimated to demonstrate a high specificity (over 95%) but a relatively low sensitivity (under 50%)[1]. Therefore, withdrawing a sufficient amount of CSF or repeating the procedure multiple times were recommended in order to avoid false-negative results[10]. In our study, CSF testing performed after the MRI was found to be positive in 9 cases (47%). This result is consistent with previous reports. Conversely, we studied 3 cases that required to be

Table 2. Univariate Analysis Log Rank.

Univariate analysis		N	Median survival (days)	P value
Age	*≥60 y*	*9*	*157*	*0.08*
	<60 y	*10*	*61*	
Gender	*Male*	*9*	*85*	*0.59*
	Female	*10*	*84*	
CSF cytology	+	*9*	*120*	*0.43*
	–	*10*	*73*	
Cervical cord lesion	+	11	45	0.017
	–	8	202	
Paralysis	+	10	60	0.014
	–	9	535	
Performance status	0-1	6	507	0.011
	2-4	13	108	
Radiation therapy	+	*11*	*61*	*0.67*
	–	*8*	*102*	
IT chemotherapy	+	9	535	<0.001
	–	10	41	

CSF: cerebrospinal fluid, IT: intrathecal

Table 3. Multivariate Analysis.

Multivariate analysis	Hazards ratio [95% CI]	P value
Existence of cervical cord lesion	4.58 [1.49-16.7]	0.007
Performance status (0-1 vs. 2-4)	3.97 [0.57-26.9]	0.16
Having paralysis	1.06 [0.21-4.27]	0.93
Administration of IT chemotherapy	0.19 [0.037-0.75]	0.016

IT: intrathecal

tested multiple times to prove positive. However, the interval between their CSF tests was more than 6 months. In other words, it could be considered as a result of disease progression since CSF tests in our cases changed to be positive and that multiple punctures might not necessarily lead to an increase in sensitivity.

In this study, 13 patients exhibited brain metastasis preceding LM, 11 of whom exhibited metastasis in the posterior fossa. Mirimanoff et al. reported that the presence of posterior fossa metastasis can cause LM and that in patients with posterior fossa metastasis, particular attention should be paid to assessing for metastasis to the spinal cord via the CSF[11]. Chow et al. described the possibility of LM resulting from dissemination via CSF pathways from posterior fossa metastasis[12]. The results of this study are consistent with those of these previous reports.

The median survival period of our patients was 59 days, which is almost the same as in previous reports[3,4]. This indicates that treatment of patients with LM is still full of challenges. In our study, treatment with intrathecal chemotherapy was associated with a good prognosis. In addition, PS was identified as a prognostic factor by univariate analysis but didn't affect the survival in multivariate analysis.

As in our study, Waki et al. reported in their retrospective study that patients who received intrathecal chemotherapy showed better survival times than those who had not[4]. A previous report also existed which showed that intrathecal chemotherapy was beneficial in patients with LM with a good PS[13]. However, our study showed PS to demonstrate no significant influence on survival on multivariate analysis. This means that PS will be a guide for the introduction of intrathecal chemotherapy. The reason for the prolongation of survival in cases with good PS is considered to be the possibility that it was easy to introduce intrathecal chemotherapy in these patients. Our study showed that intrathecal chemotherapy, not PS, affected prognosis on multivariate analysis. Introducing intrathecal chemotherapy aggressively in order to improve survival time would be desirable, although LM is an advanced disease state, so the advisability of the introduction of intrathecal chemotherapy should be judged according to the specific situation in each case.

Although no previous study examined the cervical cord lesion in analysis of related prognostic factors, the present study showed that a MRI-proven cervical cord lesion is a factor for poor prognosis. The question of what made the prognosis worse if there was a lesion at the cervical cord level is unclear. Certainly, the damage to the cervical cord due to related trauma causes dysfunction of the diaphragm and intercostal muscles involved in respiration. In this study, no patients were observed to exhibit respiratory disorder at the time of LM diagnosis, so these cervical lesions were unlikely to be directly compressing the spinal cord. However, patients' respiratory conditions worsened rapidly, and this led to death in many.

Kizawa et al. reported that direct infiltration into the spinal cord and nerve roots, which leads to the loss of nerve fibers, was observed in patients with LM. They also stated that the infiltration probably caused circular necrosis of the white matter[14]. From this report, we postulate that if a disseminated lesion at the cervical cord level occurred, infiltrating the cervical cord would be easy and cause deterioration of respiratory condition due to degeneration and necrosis of the nerve fibers.

There were some limitations in this study. First, this was a retrospective study and the number of cases was not very large. Second, the primary lesions were not specific but were a variety of different diseases. Third, we didn't discuss doses for chemotherapy or radiotherapy. These issues should be investigated further in future research.

In conclusion, existence of a cervical cord lesion is a factor for poor prognosis, while administration of intrathecal chemotherapy is seen to be a factor for good prognosis on multivariate analysis. Exhibiting paralysis and PS resulted in no significant effect on survival times.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: Hiroto Kamoda wrote and prepared the manuscript, and all of the authors participated in the study design. All authors have read, reviewed, and approved the article.

References

1. Chamberlain MC, Glantz M, Groves MD, et al. Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. Semin Oncol. 2009;36 (4):S35-45.
2. Chamberlain M, Soffietti R, Raizer J, et al. Leptomeningeal metastasis: a response assessment in neuro-oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro Oncol. 2014;16(9):1176-85.
3. Hyun JW, Jeong IH, Joung A, et al. Leptomeningeal metastasis: clinical experience of 519 cases. Eur J Cancer. 2016;56:107-14.
4. Waki F, Ando M, Takashima A, et al. Prognostic factors and clinical outcomes in patients with leptomeningeal metastasis from solid tumors. J Neurooncol. 2009;93(2):205-12.
5. Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: leptomeningeal metastases in solid tumors. Surg Neurol Int. 2013;4(4):S265-88.
6. Oechsle K, Lange-Brock V, Kruell A, et al. Prognostic factors and treatment options in patients with leptomeningeal metastases of different primary tumors: a retrospective analysis. J Cancer Res Clin Oncol. 2010;136(11):1729-35.
7. Taillibert S, Laigle-Donadey F, Chodkiewicz C, et al. Leptomeningeal metastases from solid malignancy: a review. J Neurooncol. 2005;75(1):85-99.
8. Taillibert S, Chamberlain MC. Leptomeningeal metastasis. Handb Clin Neurol. 2018;149:169-204.
9. Knafo S, Pallud J, Le Rhun E, et al. Intradural extramedullary spinal metastases of non-neurogenic origin: a distinct clinical entity or a subtype of leptomeningeal metastasis? A case-control study. Neurosurgery. 2013;73(6):923-31.
10. Glantz MJ, Cole BF, Glantz LK, et al. Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. Cancer. 1998;82(4):733-9.
11. Mirimanoff RO, Choi NC. Intradural spinal metastases in patients with posterior fossa brain metastases from various primary cancers. Oncology. 1987;44(4):232-6.
12. Chow TS, McCutcheon IE. The surgical treatment of metastatic spinal tumors within the intradural extramedullary compartment. J Neurosurg. 1996;85(2):225-30.
13. Jayson GC, Howell A, Harris M, et al. Carcinomatous meningitis in patients with breast cancer. An aggressive disease variant. Cancer. 1994;74(12):3135-41.
14. Kizawa M, Mori N, Hashizume Y, et al. Pathological examination of spinal lesions in meningeal carcinomatosis. Neuropathology. 2008;28(3):295-302.