

Factors associated with recurrent leptomeningeal metastases in patients with *EGFR*-mutated non–small-cell lung cancer

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Introduction An epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) was shown to increase the number of long-term survivors among patients with non–small-cell lung cancer (NSCLC) associated with the mutation of the *EGFR* gene.¹ However, considering the limitations of current medical technology, it is difficult to expect a cure for this disease.² In most patients, the regrowth of the primary tumor and metastases are observed. Unfortunately, depending on the site of recurrence, treatment of numerous patients with severe metastasis is difficult. Recurrent leptomeningeal metastases are particularly challenging. Meningeal metastasis is defined as a condition in which tumor cells have spread and invaded the surface of the brain and subarachnoid space, and then the ventricles and cisterns via the cerebrospinal fluid.³ The metastasis causes various neurologic symptoms and is often difficult to diagnose.³ As there is no established treatment for cancer recurrence after an effective therapy with an EGFR-TKI, patients may experience a reduced quality of life, become bedridden, and eventually die.³ Therefore, it is important to identify factors that are related to cancer recurrence. In this study, in addition to standard clinicopathological factors, we examined factors related to recurrence in the meninges, which is associated with metastases to other organs.

Patients and methods This study included patients with NSCLC and the common *EGFR* mutation, who presented to 3 tertiary hospitals from April 2009 to June 2019 and were diagnosed with distant metastasis at the time of cancer diagnosis and during the clinical course of the disease up to their death. In all 3 hospitals, the *EGFR* mutation was detected using the peptide nucleic acid-locked

nucleic acid polymerase chain reaction clamp method.⁴ Medical records and imaging studies were retrospectively reviewed. The sites of distant metastases included the lungs, bones, brain, liver, lymph nodes other than the regional ones, pleura, and peritoneum. Metastases to distant organs were revealed by diagnostic imaging such as computed tomography (CT) performed regularly and at the time of symptom presentation. The diagnosis based on the analysis of the collected malignant cell and tissue samples was also included.⁵ The recurrence of meningeal cancer was diagnosed based on various clinical symptoms, detection of malignant cells in the cerebrospinal fluid, and results of gadolinium-enhanced magnetic resonance imaging of the brain and spine.⁵

Comprehensive informed consent was obtained from each patient at the time of hospital admission for diagnostic workup of lung cancer. The study was approved by the institutional review board (decision no., NO 16–19).

Statistical analysis Logistic regression analysis was used for statistical analysis. Recurrence of NSCLC in the meninges was selected as a dependent variable, and clinicopathological factors such as age, sex, and metastases to organs other than the leptomeninges were defined as independent variables. *P* values of less than 0.05 were considered significant.

Results and discussion During the study, the *EGFR* mutation was diagnosed in 128 patients. Among them, we identified 74 patients (median age, 72 years; 48 women) who met the above selection criteria. We excluded 51 patients for the following reasons: 36 were still alive, 14 were transferred to another hospital or hospice, and

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TABLE 1 Baseline characteristics and metastatic sites of 74 patients with non–small-cell lung cancer with mutated epidermal growth factor receptor, and results of logistic regression analysis for leptomeningeal metastasis

Variable	Number of patients	Univariate analysis		Multivariate analysis	
		<i>P</i> value	OR	95% CI	<i>P</i> value
Age, <75 y/≥75 y	43/31	>0.99	0.97	0.21–4.48	0.97
Sex, female/male	48/26	>0.99	1.00	0.19–5.28	>0.99
<i>EGFR</i> mutation, Ex19/E21	44/30	0.21	3.00	0.60–15.07	0.18
Metastatic site ^a					
Lung	38/36	>0.99	2.52	0.48–13.23	0.28
Bone	41/33	0.76	3.27	0.58–18.36	0.18
Brain	42/32	0.01	6.58	1.11–38.86	0.04
Liver	51/23	>0.99	0.54	0.09–3.10	0.49
Distant lymph nodes	65/23	0.63	1.48	0.12–17.85	0.76
Pleura	31/43	>0.99	0.57	0.11–2.99	0.51
Peritoneum	67/7	<0.01	41.18	3.31–512.75	<0.01
Other sites	56/18	>0.99	0.61	0.09–4.26	0.61

a Data presented as number of patients with/without metastasis.

Abbreviations: CI, confidence interval; Ex19, exon 19 deletion; Ex21, exon 21 L858R; OR, odds ratio

1 patient was diagnosed with an uncommon mutation). Of the 74 patients, 12 developed leptomeningeal metastasis and relapsed after receiving the therapy with an EGFR-TKI. The deletion in exon 19 and the *L858R* mutation in exon 21 were found in 44 and 30 patients, respectively. The baseline characteristics of patients with *EGFR*-mutated NSCLC, information on metastatic sites, and results of the logistic regression analysis for leptomeningeal metastasis are shown in **TABLE 1**. Our analysis showed that the age of less than 75 years, female sex, and exon 19 deletion were not significant predictors of meningeal recurrence. On the other hand, a significant relationship was found between brain and peritoneal metastases and the recurrence of leptomeningeal cancer ($P = 0.04$ and $P < 0.01$, respectively).

There have been numerous studies assessing metastases to distant organs in patients with lung cancer, with the focus mainly on the frequency of metastases to individual organs.⁵ Patients with *EGFR*-mutated NSCLC are particularly interesting because some of them develop metastases to the leptomeninges.⁵ Treatment with an EGFR-TKI is a standard therapy in this population, and the number of long-term survivors has increased.¹ However, the cure has not been discovered so far,² and there is a risk of recurrence even in patients who had responded to treatment with EGFR-TKI.³ If factors related to the recurrence of leptomeningeal cancer—especially its predictors—are identified, they are likely to provide useful clinical data for future diagnosis and treatment.

In the present study, we revealed that the factors associated with the recurrence of leptomeningeal cancer were brain and peritoneal metastases. Age, sex, type of an *EGFR* mutation, and therapy with EGFR-TKI revealed no relationship with cancer recurrence at this site. It has been reported

that the incidence of leptomeningeal metastasis in molecularly unselected patients with NSCLC is not higher than 5%.⁶ In a recent review by Remon et al,³ the incidence of leptomeningeal metastasis in patients with *EGFR*-mutated NSCLC was reported at around 10%. In the present study, meningeal recurrence of cancer was seen in 12 of the 74 patients (16.2%). A review by Remon et al³ highlighted that it is unclear whether incidence of leptomeningeal metastasis is higher in patients with the *EGFR* mutation or in those treated with TKI therapy. Our results were consistent with these observations.

The recurrence of leptomeningeal cancer is associated with 2 metastatic sites: the brain and peritoneum. As for the brain metastasis, not all patients in our study had a history of recurrent leptomeningeal cancer. This might be explained by anatomical factors such as the recurrence of meningeal cancer due to brain metastasis localized near the meninges. Apart from this metastatic pathway from the brain to the leptomeninges, lymphatic and hematogenous metastatic pathways from the vertebrae, peripheral nerves, and peritoneum have been reported.⁷ Brain metastasis results in the impairment of the blood-brain barrier. If the barrier is impaired, the concentration of an EGFR-TKI in the meningeal space might be elevated, but it is not observed in practice.⁸ The exact association between reduced TKI concentrations in the cerebrospinal fluid and the recurrence of leptomeningeal cancer is yet to be established.

We showed that the recurrence of leptomeningeal cancer was also associated with peritoneal metastases. Metastatic involvement of the peritoneum is not a rare autopsy finding.⁹ The incidence of peritonitis caused by cancer was reported to reach 8% in patients with lung cancer, after exclusion of autopsy findings.¹⁰ Interestingly, peritoneal metastases, although rare, have been

recently reported in some patients with *EGFR*-mutated NSCLC.¹¹ The incidence of peritoneal metastasis in these patients might be higher as compared with that in those with *EGFR* wild-type NSCLC. Patients with an *EGFR* mutation who developed peritoneal or leptomeningeal metastasis had documented resistance to *EGFR*-TKIs at these sites.¹⁰ This suggests that such an unusual recurrence might be associated with an insufficient concentration of an *EGFR*-TKI at these sites.

It is interesting to note that recurrent peritoneal cancer was associated with meningeal recurrence. Both the pleura and the meninges are structures of a cavity. However, there was no association between pleural metastasis and leptomeningeal recurrence. Considering this, it was suggested that there should be an unknown mechanism underlying both conditions, not influenced by anatomical factors such as metastasis to another structure of a cavity. The peritoneal-plasma barrier, similar to the blood-brain barrier, was found in the peritoneum.¹² This physiologic barrier limits the absorption of drugs from blood into the peritoneal cavity. However, Patil et al¹⁰ suggested that resistance mutations in the ascitic fluid imply that poor drug penetration is unlikely to be the dominant mechanism. The similarity of the pharmacokinetics of *EGFR*-TKIs might explain the present results, although further research is needed to fully elucidate this issue. The accumulation of detailed clinical data will likely contribute to improved diagnosis and treatment of recurrent leptomeningeal cancer in patients with *EGFR*-mutated NSCLC.

Although our results are remarkable, the study has some limitations. First, although we included patients from 3 tertiary hospitals, the overall study sample was small. One of the reasons for that was longer survival time in patients with *EGFR*-mutated NSCLC due to effective treatment with *EGFR*-TKI. As for the determination of the metastatic site, this study included only patients in whom the entire course of the disease from diagnosis to death was known. However, a selection bias might have influenced the results. Second, the frequency of imaging studies and selection of an *EGFR*-TKI were at the discretion of individual pulmonologists. Therefore, prospective registry studies with regular imaging follow-up and a large number of patients are needed to confirm our results. Third, we examined the relationship between variables using logistic regression analysis without correction for multiple testing and without a replication group, but it is unclear whether this is the best possible statistical method in this case. Such limitations must be overcome in future studies.

In summary, it is important to identify specific factors related to the recurrence of leptomeningeal cancer in order to obtain useful clinical data for future diagnosis and treatment.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT HW, HS, and NH designed the study. HW, SO, and KM collected the data. HW and HS analyzed the data and prepared the manuscript. All authors approved the final version of the article.

CONFLICT OF INTEREST None declared.

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