

Factors Associated With Distant Metastasis in EGFR-mutated Non-small Cell Lung Cancer Patients: Logistic Analysis

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Abstract. *Background/Aim: The aim of this retrospective study was to identify, using logistic analysis, the factors associated with distant metastasis in non-small cell lung cancer patients carrying mutations in epidermal growth factor receptor. Patients and Methods: Patients who were diagnosed with distant metastasis at the time of diagnosis up to their death and during the period from April 2009 to March 2019, were included in this study. Clinical charts and imaging studies were reviewed. Results: A total of 64 patients during the research period. The factors associated with pleural metastasis were "female" and "no bone metastasis". The factor associated with brain metastasis was "lung metastasis". The factors associated with liver metastasis were "age under 70" and "Exon 19 deletion". Conclusion: Knowing the factors associated with distant metastasis will provide useful information to conduct targeted and efficient imaging studies.*

In epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) patients, therapy with *EGFR*-tyrosine kinase inhibitor (TKI) has increased the number of long-term survivors (1, 2). However, with current medical technology, it is difficult to expect cure (3, 4). In most patients, regrowth of the primary tumor and metastasis occur. In addition, many patients with critical metastasis are difficult to treat. Particularly, patients with brain metastasis

may become dysfunctional and develop paralysis, even if TKI or radiation results in shrinkage of the metastatic lesion (5-7). Thus, brain metastases can lead to a deterioration of quality of life. Some patients with liver metastasis, especially those with liver relapse after a good response to TKI, have a poor response to TKI therapy (8). Therefore, it is important to identify the factors that are related to metastasis to a specific organ by use of multivariate analysis.

In this study, we evaluated distant organ metastasis detected throughout the entire clinical course of NSCLC. Therefore, not only "metastasis at diagnosis" but also "metastasis appearing in the clinical course" was taken into consideration. In order to identify the factors associated with distant metastasis in *EGFR* mutated non-small cell lung cancer patients, we used Logistic analysis.

Patients and Methods

Patients, who were presented at three tertiary hospitals from April 2009 to March 2019, and were diagnosed with distant metastasis at the time of diagnosis and during the clinical course of the disease up to their death, were included in this study. Clinical charts and imaging studies were retrospectively reviewed. Distant metastasis sites included lung, bone, brain, liver, lymph nodes other than regional nodes, and pleura. Logistic regression analysis was used for statistical analysis. One organ was selected as the objective variable and the other organ metastases were considered as independent variables. By selecting several objective variables, the same analyses were performed. *p*-Values less than 0.05 were considered as statistically significant. Comprehensive informed consent was obtained from each patient at the time of admission for lung cancer diagnosis. This study was approved by Institutional Review Board.

Results

A total of 64 patients matching the above conditions during the research period were identified. The background of patients is shown in Table I. The median age of them

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Key Words: Distant metastasis, logistic analysis, epidermal growth factor receptor, non-small cell lung cancer, metastasis.

was 73, and 43 were female patients. Exon 19 deletion and Exon 21 L858R mutation were found in 37 and 27 patients, respectively. The number of patients with distant metastases to lungs, bones, brain, liver, adrenals, lymph nodes other than regional lymph nodes, and other sites were 28, 29, 26, 19, 19, 8, and 9, respectively. Therefore, the metastatic sites that could be analyzed as objective variables were pleura, brain and liver. We defined each of the three metastases as "target variables" and examined their relationship with metastases to other organs. Table II shows the analysis results when treating "pleural metastasis" as the objective variable. The factors associated with pleural metastasis were "female" and "no bone metastasis". As shown in Table III, the factor associated with brain metastasis was "lung metastasis" The factors associated with liver metastasis were "age under 70" and "Ex 19 deletion" (Table IV).

Discussion

Regarding distant organ metastasis in lung cancer, there are many studies mainly examining metastasis frequency to each organ (9-12). We have also published several studies on this subject (10-12). In particular, *EGFR* mutated NSCLC patients is of interest because some of them develop metastasis to lungs and brain (13, 14). These lung cancer patients are treated with EGFR-TKI as the 'standard therapy' and the number of long-term survivors has increased (1, 2). However, at present, cure has not been achieved (3, 4), and there is a risk of recurrence of primary and distant metastatic lesions. Long-term survivors must repeat imaging studies for metastatic lesions for longer periods, even though their frequency becomes low. If factors related to specific organ metastasis, especially factors that predict metastasis to other organs become clear, targeted and efficient imaging studies may be performed and effectively use limited medical resources.

The analysis of the results of this study revealed that the factors associated with pleural metastasis were "female" and "no bone metastasis", when treating "pleural metastasis" as the objective variable. The factor associated with brain metastasis was "lung metastasis", when treating "brain metastasis" as the objective variable. The factors associated with liver metastasis were "age under 70" and "Ex 19 deletion", when treating "liver metastasis" as the objective variable. The standard treatment for meningeal recurrence after EGFR-TKI treatment has not been established and is one of the metastatic sites of interest. In the same logistic analysis when using "meninges" as the objective variable, Exon21 L858R gene mutation was identified as a significant factor (data not shown).

Although the above results are remarkable, there were certain limitations in this study. First, this study included

Table I. Characteristics of 64 NSCLC patients with *EGFR* mutation.

Histopathological type	
Adenocarcinoma	64
Age (median, range), year	73, 50-92
Gender, M/F	21/43
<i>EGFR</i> mutation	
Exon 19 deletion/Exon 21 L858R	37/27
Metastasis (present/absent)	
Lung	28/36
Bone	29/35
Brain	26/38
Liver	19/45
Lymph nodes other than regional nodes	8/56
Other sites	9/55
Pleura	42/22

patients from three tertiary hospitals, but included a small number of patients. One of the reasons was prolongation of survival time in *EGFR* mutated NSCLC patients due to effective treatment with EGFR-TKI. Second, the frequency of imaging studies and selection of EGFR-TKI were dependent on treatment plan of each chest physician. Therefore, it is necessary to confirm our results in prospective registration studies with regularly repeated imaging examination in a large number of patients. However, it is hypothesized that the implementation of uniform treatment for patients with prolonged survival may limit patient treatment, as progress in TKI treatment is remarkable. That is, prospective registration with fixed therapy, such as administration of old generation TKI, may not be practical because patients may suffer disadvantages. Third, the validity of this research method of changing objective variables and repeating logistic analysis is questionable. Such limitations must be overcome in future studies.

In summary, identification of specific factors related to specific organ metastasis is very important. It will allow targeted and efficient imaging studies and effective use of limited medical resources.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Hiroko Watanabe, Hiroaki Satoh, Nobuyuki Hizawa designed the study; Hiroko Watanabe, Shinichiro Okauchi and Kunihiko Miyazaki collected the data; Hiroko Watanabe and Hiroaki Satoh analyzed the data; Hiroko Watanabe and Hiroaki Satoh prepared the manuscript. All Authors approved the final version for submission.

Table II. Factors associated with pleural metastasis in 64 *EGFR* mutated NSCLC patients.

Factors	Exp	95% Confidence interval	p-Value
Age, less than 70, 70 years or more	0.854	0.181-4.028	0.8418
Gender, M/F	0.174	0.339-0.773	0.0216
<i>EGFR</i> mutation			
Exon 19 deletion/Exon 21 L858R	0.391	0.223-1.761	0.2212
Metastasis			
Lung	0.920	0.028-3.796	0.9087
Bone	0.124	0.298-0.556	0.0064
Brain	1.376	0.242-6.361	0.6829
Liver	2.293	0.394-13.352	0.3559
Lymph nodes other than regional nodes	12.566	0.257-612.519	0.2020
Other sites	6.726	0.001-10.002	0.9718
Pleura	0.251	0.021-2.969	0.2725

Table III. Factors associated with brain metastasis in 64 *EGFR* mutated NSCLC patients.

Factors	Exp	95% Confidence interval	p-Value
Age, less than 70, 70 years or more	0.381	0.170-2.354	0.4949
Gender, M/F	0.633	0.248-3.469	0.9105
<i>EGFR</i> mutation			
Exon 19 deletion/Exon 21 L858R	0.927	0.553-6.496	0.3087
Metastasis			
Lung	1.896	1.246-14.738	0.0209
Bone	4.286	0.109-1.371	0.1414
Brain	0.387	0.235-3.638	0.9115
Liver	0.925	0.026-3.450	0.3319
Lymph nodes other than regional nodes	1.704	0.264-10.993	0.5752
Other sites	2.592	0.456-14.744	0.2828
Pleura	1.511	0.354-6.452	0.5772

Table IV. Factors associated with liver metastasis in 64 *EGFR* mutated NSCLC patients.

Factors	Exp	95% Confidence interval	p-Value
Age, less than 70, 70 years or more	0.224	0.570-0.879	0.0320
Gender, M/F	0.928	0.222-3.887	0.9187
<i>EGFR</i> mutation			
Exon 19 deletion/Exon 21 L858R	0.220	0.049-0.995	0.0492
Metastasis			
Lung	2.224	0.522-9.480	0.2800
Bone	1.761	0.422-7.357	0.4376
Brain	0.764	0.179-3.267	0.7168
Liver	0.270	0.018-3.971	0.3400
Lymph nodes other than regional nodes	1.252	0.180-8.703	0.8204
Other sites	1.635	0.232-11.519	0.6217
Pleura	1.734	0.319-9.419	0.5238

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Received May 6, 2019
Revised June 10, 2019
Accepted June 11, 2019