

Prognostic Factors in EGFR Mutation-positive Patients With Bone Metastases from Lung Adenocarcinoma

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Abstract

Background/Aim: This study analyzed prognostic factors in patients with lung adenocarcinoma and bone metastases who tested positive for epidermal growth factor receptor (EGFR) mutations.

Patients and Methods: We retrospectively reviewed the records of 117 patients with lung adenocarcinoma and bone metastases who were followed up at a single institution for 0.2 months to 66 months. Of these 117 patients, 45 were *EGFR* mutation-positive and further analysis was performed for these patients. Median survival times and five-year survival rates were investigated according to performance status (PS), oligometastatic status, radiotherapy and EGFR-tyrosine kinase inhibitor (TKI) administration.

Results: The five-year survival rate of *EGFR* mutation-positive patients was 9.2%, and median survival time was 22.7 months; their mean age was 69.5 years. Many *EGFR* mutation-positive patients had a PS of 2, and the median survival time showed significant differences according to PS (0/1/2 vs. 3/4) and oligometastatic status.

Conclusion: Although there was no difference in the mean survival time between patients receiving or not receiving bone radiotherapy, the treatment effectively reduced pain and prevented paralysis. As a first-line treatment in *EGFR* mutation-positive patients, first- or second-generation TKIs followed by third-generation TKIs showed favorable outcomes.

Keywords: Lung cancer, adenocarcinoma, bone metastasis, *EGFR* mutation, prognostic factor.

Introduction

As the Japanese population is rapidly aging, half will be diagnosed with cancer during their lifetime. From 1965 to

1980, more than 70% of men were smokers, possibly contributing to the high lung cancer incidence (1, 2). Lung cancer has the highest cancer mortality rate in our country, with bone metastases (BMs) developing in more than 45%



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of patients. Early in the 21st century, the median age of patients with BMs from lung cancer in Japan was reportedly 59.6 years (3). In our current series, the median age was 69.9 years, approximately 10 years older. The histological classifications of lung cancer, from most to least common, is adenocarcinoma (50%-60%), squamous cell carcinoma (25%-30%), small cell carcinoma (10%-15%), and large cell carcinoma (approximately 5%). Neuroendocrine tumors that were added to the 2015 World Health Organization classification, including small cell carcinoma, large cell endocrine tumor, and carcinoid, are cancers with extremely high malignant potential and poorer outcomes (4). In adenocarcinoma, epidermal growth factor receptor (*EGFR*) mutations are present in approximately 45% of tumor tissues from primary tumors and metastases in Asian women and non-smokers (5, 6). Among the *EGFR* mutations, exon 19 deletion (Del 19; 44.8%) and exon 21 L858R (L858R; 39.8%) are the most common, with a small number of other mutations, such as exon 20 insertion (Ins 20; 5.8%) and exon 18 mutation (G719X; 3.1%) (7, 8). Due to the widespread use of positron emission tomography-computed tomography (PET-CT) and other imaging modalities (9, 10), patients with BMs are often managed by orthopedists. The survival of *EGFR* mutation-positive patients is better with the use of *EGFR*-tyrosine kinase inhibitors (TKIs) (11), and the mainstay for managing BMs is local treatment, such as radiotherapy (RT) and surgery. Furthermore, when hypercalcemia is also present, it is regarded as a skeletal-related event (SRE) (12). However, herein our focus is the survival times of patients with BMs in relation to prognostic factors. Thus, we assessed post-treatment outcomes of *EGFR* mutation-positive patients with BMs from lung adenocarcinoma at our institution.

Patients and Methods

Patients. We retrospectively reviewed 163 patients at our institution with lung carcinomas with BMs from October 2017 to September 2023. Of these, 24 and 22 patients had BMs from squamous cell carcinoma and small cell

carcinoma, respectively, leaving 117 patients with BMs from lung adenocarcinoma involved in the study, including 18 patients who underwent primary lung surgery. Patients were followed up in our department for an average of 17.3 months (range=0.2-66 months); however, one *EGFR* mutation-positive patient, three *EGFR* mutation-negative patients, and two patients with other gene mutations were lost to follow-up. Four patients had stage IIIB tumors, 11 had stage IVA tumors, and 102 patients had stage IVB tumors. Forty-five adenocarcinoma patients had *EGFR* mutations, including Del 19, L858R, Ins 20, G719X, and resistance-conferring thr790met (T790M). Sixty-one patients were *EGFR* mutation-negative, and other genes, including anaplastic lymphoma kinase fusion, Kirsten rat sarcoma viral oncogene homolog mutation, ROS oncogene 1 fusion, and mesenchymal-epithelial transition factor mutation, were detected in 11 patients.

Prognostic factors. The patients who were *EGFR* mutation-positive were divided into three groups according to Eastern Cooperative Oncology Group-performance status (PS), *i.e.*, '0/1', '2', and '3/4'. Cases with BMs were divided into oligometastatic and multiple metastatic states, and metastasis sites were divided into spine (including sacrum), thorax (ribs, scapula, sternum), pelvis (iliac, pubic, ischium), and extremities (femur, humerus, tibia). Other distant metastases included metastases to the brain, liver, adrenal glands, and kidneys.

Diagnosis of BMs and SREs. BMs were detected simultaneously with lung adenocarcinoma in 49 patients (41.9%). Pathological diagnosis was mostly based on tissue collected from the primary tumors or cervical lymph node metastases. Tissue sampling of the primary tumor or another bone metastatic site was initially insufficient in eight patients (6.8%), necessitating biopsy of the BM; three with spine, two with pubis, and one each with ischium, scapula and femur involvement. Five patients underwent CT-guided biopsies, and three others underwent incisional biopsies. All patients were pathologically diagnosed as having lung adenocarcinoma,

and the BMs were subjected to gene panel testing in four patients. Once lung cancer was diagnosed, PET-CT and brain magnetic resonance imaging (MRI) were performed to determine the stage, and if there was specificity of pooling which allowed the detection of BMs on PET-CT, the patient was referred to our department at our institute, where clinical symptoms and the presence or absence of osteolysis were examined using CT. Compression from the spine to the spinal cord was confirmed using a whole-spine MRI. SRE was present in 77 of the 117 patients with adenocarcinomas (65.8%), of whom 27 patients (60%) had *EGFR* mutation-positive BMs.

Treatments. RT was administered to 25 patients (55.6%) with *EGFR* mutation-positive BMs. RT was administered to sites of oligometastatic disease, osteolysis, sites causing symptoms, or sites that may be involved in later developed symptoms. No patient with spinal metastases received RT for spinal flattening or compression, and no patient underwent spinal surgery. Twelve patients with lung cancer bone metastases underwent surgery, but only two were *EGFR* mutation-positive and these patients underwent intramedullary nailing and femoral head replacement. The most frequently-administered *EGFR*-TKIs were: first-generation, gefitinib and erlotinib; second-generation, afatinib; and third-generation, osimertinib. If resistance to TKIs was observed, cytotoxic anticancer drugs, such as carboplatin and pemetrexed, as well as immune checkpoint inhibitors, such as bevacizumab and atezolizumab, were administered. *EGFR*-TKIs were administered to 44 *EGFR* mutation-positive patients (97.8%). In this group, we investigated which TKI, as first-line treatment, influenced outcomes.

Median survival times and survival rates. These groups and subgroups were compared, employing median survival time and the Kaplan–Meier method for five-year survival rates.

Ethical standards. The study was approved by the ethics committee of Kasukabe Medical Center (approval number: KMC P2023-001, May 23, 2023).

Table 1. *Distribution of patients with bone metastases from lung adenocarcinoma (n=117).*

Prognostic factor	Median age [SD], (range), years	No. of patients (%)
Adenocarcinoma	69.9 [10.1], (45-89)	117
<i>EGFR</i> mutation-positive	69.5 [11.7], (45-89)	45 (38.5)
Exon 19 deletion (Del 19)	68 [11.7], (50-88)	25 (55.6)
Exon 21 L858R (L858R)	73.5 [12.4], (45-89)	17 (37.8)
Exon 20 insertion (Ins 20)	67.5	2 (4.4)
Exon 18 (G719X)	63	1 (2.2)
Thr790Met (T790M)*	68.9	10 (22.2)
<i>EGFR</i> mutation-negative	69.5 [9.3], (45-89)	61 (52.1)
ALK fusion	69 (68-70)	3 (2.6)
KRAS mutation	73.5 (65-80)	6 (5.1)
ROS1 fusion	73	1 (0.9)
MET mutation	89	1 (0.9)

*Resistance-conferring T790M. SD: Standard deviation; *EGFR*: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; KRAS: Kirsten rat sarcoma viral oncogene homolog; ROS1: c-ros oncogene-1; MET: mesenchymal-epithelial transition factor.

Statistical analysis. Cox proportional hazards survival models were obtained employing logistic regression analysis in *EGFR* mutation-positive patients. Multivariate analyses using the log-rank test were conducted, including age, sex, PS 0/1/2 vs. 3/4, and administration of first/second-generation vs. third-generation TKIs as first-line treatment, as variables. We used IBM SPSS version 25 software (IBM Corporation; Armonk, NY, USA).

Results

The median (standard deviation) age at the time of BM detection was 69.9 (10.1) years (range=45-89 years) for all adenocarcinomas, and there was no difference in median age with *EGFR* mutation status (Table 1).

Survival rates for *EGFR* mutation status in patients with BMs. In all 117 patients with adenocarcinoma, the one- and two-year survival rates were 56.4% and 38.0%, respectively (Kaplan–Meier method). Of the total of 106 patients whose *EGFR* mutation status was determined, the 45 patients who were *EGFR* mutation-positive had one- and two-year survival rates of 70.8% and 51.8%,

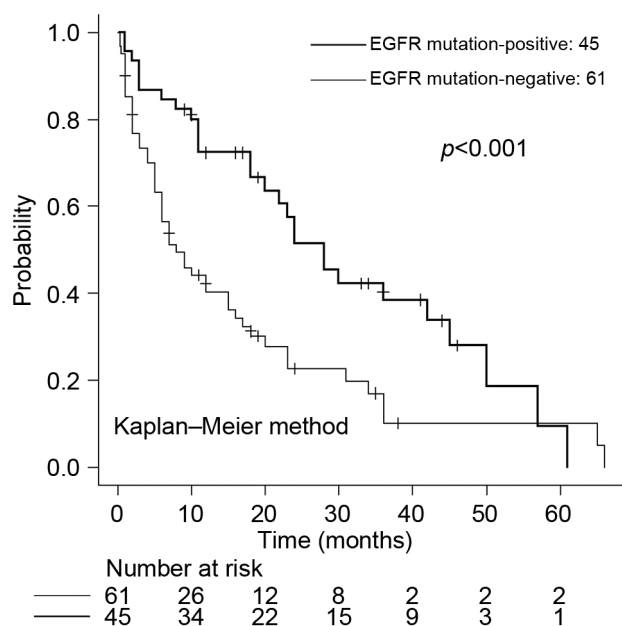


Figure 1. Kaplan-Meier curves showing all 117 patients with bone metastases from adenocarcinoma, of whom 45 were positive for epidermal growth factor receptor (*EGFR*) mutations and 61 were negative. The survival rate for *EGFR* mutation-positive patients was significantly better than that for *EGFR* mutation-negative patients ($p<0.001$).

respectively, whereas the 61 patients who were *EGFR* mutation-negative, had rates of 41.0% and 22.9%, respectively ($p<0.001$) (Figure 1).

Median survival time and survival rate based on prognostic factors. For all 117 patients with adenocarcinoma, the median survival time was 16.6 months. Of these, the 45 patients who were *EGFR* mutation-positive had a median survival time of 22.4 months, compared to the 61 *EGFR* mutation-negative patients with a median survival time of 12.6 months. A comparison of patients with the Del 19 and L858R mutations revealed that the median survival time and survival rates tended to be slightly better in those with the former mutations ($p=0.22$). Patients with the T790M resistance mutation had the longest median survival of 38.0 months (Table II).

Overall, adenocarcinoma was more common in men (60.7%), whereas *EGFR* mutation-positive patients were

more commonly women (60%). The median survival time of patients with a PS 0/1 or 2 was significantly longer than that of patients with a PS of 3/4 ($p<0.02$). The 12 patients (26.7%) with oligometastatic lesions had a significantly better median survival of 31.3 months compared to 19.2 months for those with multiple metastases ($p<0.03$). The median survival time for patients where sites of BMs included the spine, thorax, pelvis, and limbs, ranged from 22.4 to 27.4 months, while the median survival time for patients with other organ metastases, including the brain, liver, adrenal glands, and kidneys, ranged from 22.5 to 42 months. There was no significant difference in outcome depending on the presence or absence of brain metastasis accompanied by BMs (Table II). The median survival time of the 27 *EGFR* mutation-positive patients with SRE was 22.7 months, with the majority receiving RT. Two patients with impending or pathologic fractures of the extremities underwent surgery and RT, with a median survival of 31 months. Biopsies and panel tests were performed in four patients for BM and impending or pathological fractures, and two patients were found to be *EGFR* mutation-positive, enabling early treatment.

Median survival time according to RT for BMs. RT was performed in a relatively large number of patients for BMs from adenocarcinoma. There were no significant differences in the median survival time between patients receiving or not receiving RT among patients with adenocarcinoma ($p=0.50$) or those positive for the *EGFR* mutation ($p=0.37$; Table III).

Median survival time with *EGFR*-TKI as first-line treatment. Chemotherapy was administered to 104 of the total 117 patients, including 44 of 45 patients (97.6%) who were *EGFR* mutation-positive, and 51 of 61 (83.6%) who were *EGFR* mutation-negative. Thirteen (11.1%) of the patients with adenocarcinoma were unable to tolerate chemotherapy and instead received palliative care and treatment for infections and died within 3 months. The survival rates of those with Del 19, L858R, Ins 20, and G719X mutations are shown in Table II. As first-line

Table II. Median survival times and survival rates (Kaplan–Meier method) according to prognostic factors for patients with epidermal growth factor receptor (*EGFR*) mutation-positive bone metastases.

Prognostic factor	No. of patients (%)	Median survival, months (no. alive/dead/dropouts)	Survival rates (%)					p-Value
			1-year	2-year	3-year	4-year	5-year	
(K-M survival %)								
Histology								
Adenocarcinoma	117	16.6 (29 alive/82 dead/6 dropouts)	56.4	38	22.7	17.9	10.7	
EGFR mutation status								
EGFR mutation-positive	45 (38.5)	22.4 (17 alive/27 dead/1 dropout)	70.8	51.8	37.7	27.5	9.2	<0.001
Del 19	25 (55.6)	25.4 (9 alive/15 dead/1 dropout)	79.5	62.4	49.6	37.2	12.4	0.22*
L858R	17 (37.8)	20.4 (5 alive/12 dead)	63.7	46	28.3	18.9	-	
Ins 20	2 (4.4)	5.5 (1 alive/1 dead)						
G719X	1 (2.2)	16 (1 alive)						
T790M	10 (22.2)	38.0 (4 alive/6 dead)	100	88.9	77.8	62.2	20.7	
EGFR mutation-negative	61 (52.1)	12.6 (9 alive/49 dead/3 dropouts)	41	22.9	10.3	5.2	5.2	
ALK	3	26 (2 alive/1 dead)	100	100	-			
KRAS	6	14.3 (2 alive/2 dead/2 dropouts)	83.3	41.7	-			
ROS1	1	2 (1 dead)	0					
MET	1	3 (1 dead)	0					
Sex								
Female	27 (60)	22.9 (6 alive/20 dead/1 dropout)						0.4
Male	18 (40)	21.7 (10 alive/8 dead)						
Performance Status (PS)								
PS 0/1	11 (24.4)	26.4 (2 alive/9 dead)						<0.02**
PS 2	20 (44.4)	26.3 (6 alive/13 dead/1 dropout)						
PS 3/4	14 (31.1)	13.8 (6 alive/8 dead)						
Metastatic involvement								
Oligometastatic state	12 (26.7)	31.3 (8 alive/4 dead)						<0.03
Multiple	33 (73.3)	19.2 (9 alive/23 dead/1 dropout)						
Metastatic site								
Spine	41 (91.1)	22.4 (10 alive/30 dead/1 dropout)						
Thorax	27 (60)	27.4 (10 alive/17 dead)						
Pelvis	22 (48.9)	22.7 (8 alive/14 dead)						
Limb	12 (26.7)	25.2 (4 alive/8 dead)						
Brain	23 (51.1)	23.0 (4 alive/18 dead/1 dropout)						
Liver	4 (8.9)	22.5 (2 alive/2 dead)						
Adrenal gland	5 (11.1)	24.8 (2 alive/3 dead)						
Kidney	1 (2.2)	42 (1 dead)						

*Comparison of Del 19 and L858R; **Comparison of PS 0/1/2 and 3/4. K-M: Kaplan–Meier; PS: performance status; ALK: anaplastic lymphoma kinase; KRAS: Kirsten rat sarcoma viral oncogene homolog; ROS1: c-ros oncogene-1; MET: mesenchymal-epithelial transition factor.

treatment for *EGFR* mutation-positive patients, the third-generation TKIs were used in 17 patients, while first- or second-generation TKIs were given to 16 patients (gefitinib [n=4], erlotinib [n=9], and afatinib [n=3]), and cytotoxic anticancer drugs and/or immune checkpoint drugs were given to 11 patients, achieving median survival times of 17.5, 27.3, and 26.9 months, respectively. As initial treatment, administration of a third-generation TKI after a first- or second-generation TKI was favorable ($p<0.05$).

Third-generation TKIs were often administered after the first- or second-generation TKI became ineffective. Eleven patients received treatment with cytotoxic anticancer drugs or immune checkpoint drugs initially, and then first- or second-generation TKIs were administered after the results of gene panel testing were available, followed by third-generation TKIs, which were effective. Ten patients who received first- or second-generation TKIs were positive for the resistance-conferring T790M mutation and received

Table III. Median survival time in all adenocarcinoma patients, including epidermal growth factor receptor (EGFR) mutation-positive and -negative patients, according to radiotherapy for bone metastases.

Prognostic factor	Radiotherapy	No. of patients (%)	Median survival, months (no. of patients alive/dead/dropouts)	p-Value
Adenocarcinoma	Yes	73 (62.4)	16.7 (17 alive/53 dead/3 dropouts)	0.5
	No	44 (37.6)	16.5 (12 alive/29 dead/3 dropouts)	
EGFR mutation positive	Yes	25 (55.6)	21.7 (8 alive/17 dead)	0.37
	No	20 (44.4)	23.3 (8 alive/11 dead/1 dropout)	
EGFR mutation negative	Yes	42 (68.9)	14.2 (6 alive/34 dead/2 dropouts)	0.09
	No	19 (31.1)	9.1 (3 alive/15 dead/1 dropout)	

third-generation TKIs with the higher median survival time of 38.3 months; among these, six patients with Del 19 had the highest survival time of 43.7 months (Table IV).

Multivariate analysis and results according to clinical factors. The Cox proportional hazards model was used to estimate the hazard ratio and confidence interval. While there were no significant differences according to age ($p=0.48$) or sex ($p=0.17$), there was a clear significant difference between a PS of 0/1/2 and 3/4 ($p<0.02$), and between first/second-generation TKIs and third-generation TKIs as first-line treatment ($p<0.01$; Table V).

Discussion

Lung cancer has the second highest frequency of any malignancy in Japan but has the largest number of mortalities. The major lung cancer types are roughly divided into non-small cell and small cell carcinoma, with respective reported BM rates of 48% and 40%, with nearly half being detected at the time of initial staging (12). The proportions of each gene type in adenocarcinoma are approximately 45% for EGFR mutations (2, 5-7, 11), 3%-5% for the anaplastic lymphoma kinase fusion gene (13, 14), with the ROS oncogene 1 fusion (15), B-Raf proto-oncogene mutation (16) and Kirsten rat sarcoma viral oncogene homolog mutation (5) genes accounting for 1%-2% each. These frequencies are similar to those noted in our present series. Sugiura *et al.* (3) reported 118 patients with BMs

from lung cancer whose one-year survival rate was 31.6%. In 14 patients who received gefitinib, the one-year survival rate was 84.6% and the two-year rate approached 40%. In our study, for the entire group of 117 patients with adenocarcinoma, the one-year survival rate was 55.9%, and the one-year survival rate of the 45 EGFR mutation-positive patients who received EGFR-TKIs was 70.8%, while the two-year rate was 51.8%. Patients with the Del 19 vs. L858R genetic abnormality were compared. The respective one-year survival rates were 79.5% vs. 63.7%, revealing slightly better outcomes with the Del 19 mutation ($p=0.22$). EGFR mutation-positive patients included those with Ins 20 and G719, which were associated with a slightly lower survival rate.

As mentioned above, the median age of patients with BMs from lung cancer has risen by roughly 6-10 years, compared to the early 21st century (3, 17). EGFR mutation-positive adenocarcinomas were more common in women, and survival was good for both sexes. PS is usually classified into 0/1 and 2/3/4 in the literature (3). However, we divided the patients into PS 0/1 and 2 vs. 3/4 because chemotherapy is generally administered to patients with a PS of at least 2. There was no significant difference between patients with a PS of 0/1 vs. 2. Furthermore, EGFR mutation-positive patients with a PS of 2 or better had improved outcomes compared to those with a PS of 3/4 ($p<0.02$). Although solitary metastases are rare, surgery is recommended due to their favorable prognosis (3), and in our present series, patients with an

Table IV. Median survival time with *EGFR*-TKI as first-line treatment in epidermal growth factor receptor (*EGFR*) mutation-positive patients.

Prognostic factor	No. of patients (%)	Median survival, months (no. of patients alive/dead/dropouts)	<i>p</i> -Value
EGFR mutation-positive			
Chemotherapy	44	23.4 (16 alive/27 dead/1 dropout)	
No chemotherapy	1	2.0 (1 dead)	
TKIs generation			<0.05**
Third-generation TKIs	17	17.5 (2 alive/15 dead)	
First- or second-generation TKIs	16	27.3 (7 alive/9 dead)	
Cytotoxic anticancer/immune drugs*	11	26.9 (7 alive/3 dead/1 dropout)	
Mutation type: Del 19			0.085**
Third-generation TKIs	11	18.8 (2 alive/9 dead)	
First- or second-generation TKIs	9	30.9 (3 alive/6 dead)	
Cytotoxic anticancer/immune drugs	5	29.8 (4 alive/0 dead/1 dropout)	
Resistance T790M	6	43.7 (2 alive/4 dead)	
Mutation type: L858R			0.12**
Third-generation TKIs	6	15.2 (6 dead)	
First- or second-generation TKIs	7	22.6 (4 alive/3 dead)	
Cytotoxic anticancer/immune drugs	4	24.5 (1 alive/3 dead)	
Resistance T790M	4	27.5 (2 alive/2 dead)	
Mutation type: Ins 20			
Immune checkpoint drugs	1	9.0 (1 alive)	
Mutation type: G719X			
Immune checkpoint drugs	1	16.1 (1 alive)	
Resistance T790M			
Third-generation TKIs	0		
First- or second-generation TKIs	8	38.3 (3 alive/5 dead)	
Cytotoxic anticancer drugs	2	37.0 (1 alive/1 dead)	
EGFR mutation-negative			
Chemotherapy	51	15.1 (9 alive/41 dead/1 dropout)	
No chemotherapy	10	1.6 (8 dead/2 dropouts)	

*Initially, these agents were used first, and depending on the results of gene panel testing, first- or second-generation TKIs were administered, followed by third-generation TKIs. **Comparison of 3rd- and 1st- or 2nd-generation TKI. EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor.

oligometastatic state had better outcomes ($p < 0.02$) (18). The usual sites of BMs are the spine and thorax, and EGFR mutation-positive patients with involvement of these sites had better outcomes overall. Brain metastases were detected early and treated with gamma knife radiosurgery or whole-brain RT. There was no difference in outcomes between the presence or absence of brain metastases. In addition, the median survival time tended to decrease with liver metastases regardless of *EGFR* mutation status (3). When a cancer patient is in pain, it is necessary to determine where the pain is coming from and to confirm the site of metastasis using PET-CT, CT, MRI, or radionuclide imaging (9, 10).

For BMs, the RT regimen is usually 30 gray (Gy)/10 fractions (Fr), but 20 Gy/5 Fr and 8 Gy/1 Fr, both of which show good efficacy, can also be administered. Stereotactic body RT was recently reported to be more effective for oligometastatic lesions (18, 19). We performed RT as early as possible and in as many patients as possible, such that SREs occurred at a high frequency of 65.8%. Intramedullary nails, femoral head prosthesis, or spinal fusion are used when pain is present in the limbs or spine and osteolytic changes are seen on CT, though even asymptomatic patients who are EGFR mutation-positive and have significant osteolysis in the spine or extremities can be treated with RT and bone-modifying drugs (20).

Table V. Multivariate analysis of selected clinical factors in patients with bone metastases from epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma.

Log Rank (Mantel-Cox)		
Prognostic factor	Hazard ratio (95%CI)	p-Value
Age (≥ 70 vs. < 70)	1.02 (0.97-1.06)	0.48
Sex (female vs. male)	0.53 (0.22-1.30)	0.17
PS (0/1/2 vs. 3/4)	0.31 (0.12-0.78)	< 0.02
1 st /2 nd - vs. 3 rd -generation TKIs	0.29 (0.12-0.71)	< 0.01

CI: Confidence interval; PS: performance status; TKI: tyrosine kinase inhibitor.

Patients with impending spinal paralysis benefit from emergency RT and bone-modifying drugs, with rigid corset placement achieving symptom relief approximately one to two weeks later. Examining median survival time in patients with or without RT to BM sites revealed no difference, but RT was found to be useful for local control in the early stages (18).

In recent years, EGFR-TKIs have been used for EGFR mutation-positive patients, providing rapidly improved outcomes, and these agents are also effective against BMs (11). However, several issues have yet to be resolved regarding the optimal administration methods for these TKIs. First-, second-, or third-generation TKIs are often used as first-line treatment. Resistance to these drugs develops after about 12 months (7, 21-23). In our series, as first-line treatment, cytotoxic anticancer drugs and/or immune checkpoint drugs were often administered before panel testing results had become available, followed by first-, second-, or third-generation TKIs. When considering median survival times according to the order of administration of these TKIs, patients who received a third-generation TKI after developing resistance to a first- or second-generation TKI showed significantly better outcomes ($p < 0.05$) (11). Akamatsu *et al.* (24) treated 41 patients with the T790M mutation with third-generation TKIs, but the one-year survival rate was less than 60%. Although the number of patients developing the T790M resistance-mutation was small in our study, only 10 patients, the median survival time was significantly longer at 38.0 months (21, 25, 26).

Study limitations. As a retrospective analysis conducted at a single institution, there may be inherent selection biases, limiting the generalizability of our findings. A multi-center or prospective study with a larger sample size would be needed to confirm our results.

While we identified prognostic factors, confounding variables were not fully accounted for. These factors may have influenced survival outcomes but were not systematically analyzed in this study.

Conclusion

This study focused on EGFR mutation-positive patients with BMs and showed that a PS of 0/1/2, and administration of first- or second-generation TKIs as first-line treatment were significantly better prognostic factors. To maintain PS, it was necessary to detect painful bone metastatic lesions or sites that could cause fractures or paralysis and perform emergency radiotherapy or surgery. Although the primary tumor could not be diagnosed in four patients, panel testing was performed with bone biopsy, and as the EGFR mutation was positive, early treatment was possible and should be considered in such cases.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

The first draft of the manuscript was written by Shunzo Osaka, MD and all Authors commented on the manuscript. Dr. Junzo Kawashima collected and organized all the patients with bone metastasis of lung cancer, and Drs. Ryoma Kaguchi and Naoki Toda reported part of this paper at a conference. Drs. Akira Kisohara, Shumei Kan and Kohei Tagawa treated these patients as the main doctor, and Dr. Yoshiaki Tanaka performed radiotherapy, and each of them proofread this article. Drs. Toshio Kojima and Takako Nagai provided statistical analysis and

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