Lung Cancer 146 (2020) 236–243

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Key prognostic factors for *EGFR*-mutated non-adenocarcinoma lung cancer patients in the Japanese Joint Committee of Lung Cancer Registry Database

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ARTICLE INFO

Keywords:
Lung cancer registry
EGFR mutation
Non-adenocarcinoma
EGFR-TKI
Prognostic factor

ABSTRACT

Introduction: The efficacy of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) for *EGFR*-mutated non-adenocarcinoma (ADC) non-small cell lung cancer patients is not well established. Herein, we investigated key prognostic factors influencing the efficacy of EGFR-TKIs in these patients.

Methods: A total of 12,320 lung cancer patients pathologically diagnosed in 2012 at teaching hospitals in Japan were retrospectively selected. The follow-up survey was closed in 2016.

Results: *EGFR*-mutated non-ADC patients were more prone to malignant pleural effusion (MPE) and distant metastasis than ADC patients (P = 0.071 and 0.022, respectively). *EGFR*-mutated ADC patients were likely to have a longer median overall survival (OS) than non-ADC patients [hazard ratio (HR) 1.3 (95 % CI, 0.97–1.8, P = 0.072)—29.5 months (95 % CI, 27.9–31.1 months) versus 19.5 months (95 % CI, 10.8–28.2 months) (P = 0.068)]. There was no significant difference in median OS between *EGFR*-positive ADC and non-ADC patients receiving treatment with first-generation EGFR-TKI. Among *EGFR*-positive non-ADC patients, the median OS was significantly longer for patients receiving EGFR-TKI treatment than for those who did not [HR 4.5 (95 % CI, 2.1–9.8, P < 0.001)—25.5 months (95 % CI, 8.1–42.9 months) versus 7.5 months (95 % CI, 3.4–11.6 months) (P < 0.001)]. While there was no significant difference in the median OS for ADC patients with either 19 del or L858R mutations, the median OS was significantly longer for *EGFR*-mutated non-ADC patients with 19 del than for those with L858R mutation (HR 3.2 [95 % CI, 1.5–6.9, P = 0.004]; it was not reached for 19 del and was 15.5 months for L858R [95 % CI, 6.6–24.4 months], P = 0.002).

Discussion: *EGFR*-mutated non-ADC patients were more prone to MPE and distant metastasis. Both ADC and *EGFR* del19-positive non-ADC patients can benefit from EGFR-TKI treatment, whereas *EGFR* L858R-positive non-ADC patients might require different therapeutic options.

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https://doi.org/10.1016/j.lungcan.2020.06.015
Received 17 April 2020; Received in revised form 9 June 2020; Accepted 12 June 2020

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. The discovery of epidermal growth factor receptor (*EGFR*) as a driver oncogene in adenocarcinoma (ADC) and the discovery of the efficacy of tyrosine kinase inhibitors (TKIs) in patients with *EGFR* mutations have revolutionized lung cancer therapy [1–4].

The number of *EGFR*-mutated ADC patients is relatively high, while non-ADC patients harboring *EGFR* mutations are scarce [5,6]. Because of the low frequency of *EGFR*-mutated non-ADC non-small cell lung cancer (NSCLC) cases, there is little evidence on the efficacy of EGFR-TKIs on the overall survival (OS) of these patients. Generally, the effect of EGFR-TKIs on these patients is known to be limited; however, some patients have good response to some extent [7].

The aims of this study were, first, to investigate the efficacy of EGFR-TKIs on OS of *EGFR*-mutated non-ADC patients through comparison with *EGFR*-mutated ADC patients, and second, to identify the key prognostic factors influencing the efficacy of first-generation EGFR-TKIs (gefitinib or erlotinib) for these patients.

The present study is the sixth registry study of cases in the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) history in which data of lung cancer patients pathologically diagnosed in 2012 were collected.

2. Materials and methods

2.1. Study population

The JJCLCR performed a nationwide retrospective study of lung cancer patients diagnosed in 2012, who received non-surgical treatment. The committee asked 846 teaching institutions in Japan to join this study, among which 314 institutions (37.1 %) participated. A total of 14,260 patients were considered as study subjects. The exclusion criteria were as follows: (1) no data input, (2) stage not confirmed, (3) lost to follow-up, and (4) ineligible.

This registry was opened on January 1, 2012, and the follow-up survey was closed on April 30, 2016. The registration of patient information was performed through a website system, as described in a previous registry study [8].

The registry followed the ethical guidelines for epidemiologic studies. This study was approved by the review board of Osaka University Medical Hospital (approval No. 15,321).

2.2. Clinical characteristics

The following clinical characteristics were included in our analyses: age at diagnosis, gender, smoking history, ECOG performance status (PS), the presence or absence of malignant pleural effusion (MPE), distant metastasis (lung, liver, bone, brain, and adrenal gland), and types of *EGFR* mutations (exon 19 deletion [19 del], exon 21 L858R [L858R], and others).

Patients who reported to have never smoked in their lifetime were defined as non- smokers, those who had smoked within 1 year of diagnosis were categorized as current smokers, and the rest were considered former smokers.

2.3. Clinical responses

Clinical responses to EGFR-TKIs were evaluated based on interpretation of the progression report in accordance with the Response Evaluation Criteria in Solid Tumors (version 1.1) [9]. Notably, radiologists did not necessarily detail each target lesion across all the centers.

Tumor responses were defined as follows: a complete response (CR; the disappearance of all target lesions), a partial response (PR; ≥ 30.0 % reduction in the sum of the diameters of the target lesions), progressive disease (PD; ≥ 20.0 % increase in the sum of the diameters of the target lesions), and stable disease (SD; insufficient shrinkage or expansion to qualify as a PR or PD). In the absence of measurable disease, unequivocal progression was defined as that required to declare clinically PD as PD.

Table 1
Comparison of patient characteristics between EGFR-mutated adenocarcinoma and non-adenocarcinoma.

Characteristics	Adeno (n = 1709)	Non-Adeno (n = 77)	P value
Age (yr)			0.785
Median (range)	68.0 (23–99)	69.0 (32–88)	
Gender			< 0.001
Male	626 (36.6 %)	44 (57.1 %)	
Female	1083 (63.4 %)	33 (42.9 %)	
Smoking history			0.182
Never	1009 (59.0 %)	39 (50.6 %)	
Former	421 (24.6 %)	26 (33.8 %)	
Current	279 (16.3 %)	12 (15.6 %)	
PS (ECOG)			0.841
0,1,2	1548 (90.6 %)	71 (92.2 %)	
3,4	161 (9.4 %)	6 (7.8 %)	
Malignant pleural effusion			0.071
yes	1207 (70.6 %)	62 (80.5 %)	
no	502 (29.4 %)	15 (19.5 %)	
Distant metastasis			0.022
yes	1264 (74.0 %)	66 (85.7 %)	
no	445 (26.0 %)	11 (14.3 %)	
Lung metastasis			0.493
yes	224 (13.1 %)	12 (15.6 %)	
no	1475 (86.3 %)	65 (84.4 %)	
Liver metastasis			0.191
yes	184 (10.8 %)	12 (15.6 %)	
no	1525 (89.2 %)	65 (84.4 %)	
Bone metastasis			0.484
yes	770 (45.1 %)	38 (49.4 %)	
no	939 (54.9 %)	39 (50.6 %)	
Brain metastasis			0.258
yes	532 (31.1 %)	19 (24.7 %)	
no	1177 (68.9 %)	58 (75.3 %)	
Adrenal metastasis			0.371
yes	126 (7.4 %)	8 (10.4 %)	
no	1583 (92.6 %)	69 (89.6 %)	
Types of EGFR mutation			0.561
19 del	853 (49.9 %)	34 (44.2 %)	
L858R	753 (44.1 %)	39 (50.6 %)	
Others	103 (6.0 %)	4 (5.2 %)	

Abbreviations: EGFR, epidermal growth factor receptor; yr, year; PS, performance status; 19 del, exon 19 deletion; L858R, exon 21 L858R.

2.4. Data examination

Following closure of the registration, the data were carefully examined. If inconsistent or conflicting data, double registration, incomplete information, or outliers were found, the registration office made corrections after inquiring at the respective hospitals.

2.5. Statistical analyses

Statistical analyses using the Pearson's chi-square test, Fisher's exact test, and student's *t*-test were performed. The survival period was calculated on the basis of the number of months from the first diagnosis to death. Survival curves were estimated according to the Kaplan–Meier method for clinical variables. Differences in survival were tested using the log-rank method. A two-sided $P < 0.05$ was considered statistically significant for all the tests. All statistical analyses were performed using the SPSS software program, version 23.0 (SPSS Inc., Chicago, Illinois), for Windows.

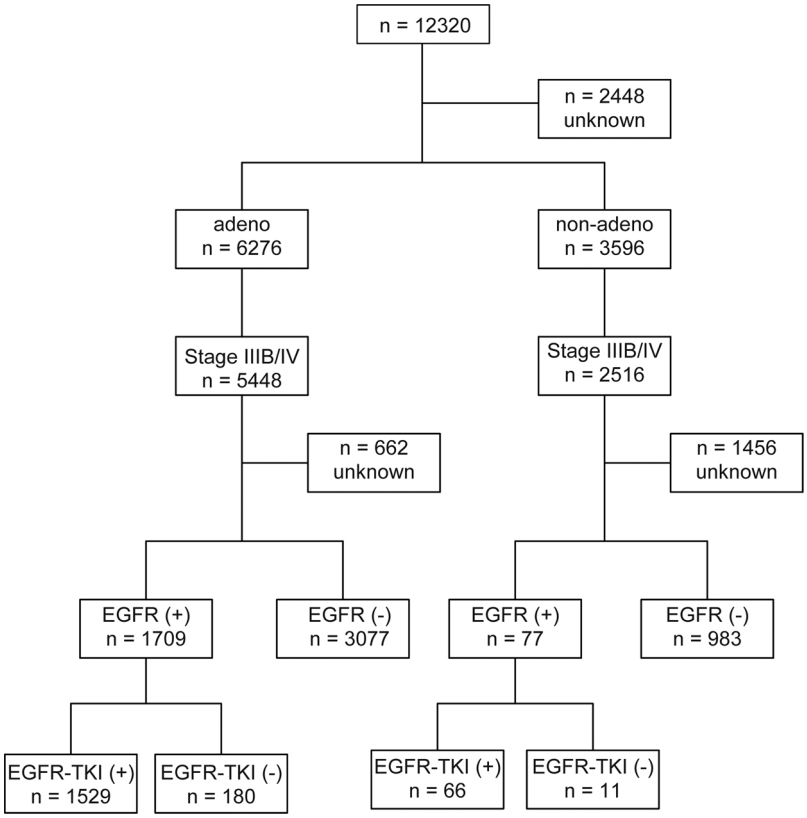

Fig. 1. Flow diagram of study participants.
Abbreviations: adeno, adenocarcinoma; EGFR, epidermal growth factor receptor; TKI, (EGFR) tyrosine kinase inhibitor; n = number.

3. Results

3.1. Clinical characteristics of the study population

A total of 14,260 patients were registered from 314 institutions in Japan. Of these, 1940 patients were excluded because of no data input (n = 244), stage not confirmed (n = 188), lost to follow-up (n = 216), and ineligible (n = 1292). Thus, finally 12,320 patients were enrolled. Of 5448 Stage IIIB or IV ADC patients, 1709 patients (n = 1709/5448, 31.4 %) had an *EGFR* mutation-positive status. Of these patients, 1529 patients received EGFR-TKI therapy. Of 2516 Stage IIIB or IV non-ADC patients, 77 patients (n = 77/2516, 3.1 %) had an *EGFR* mutation-positive status. Of these patients, 66 patients received the EGFR-TKI therapy. The details about the proportion of each *EGFR* mutation in these patients are presented in Table S1.

Histological subtypes of Stage IIIB or IV *EGFR*-mutated non-ADC included squamous cell carcinoma (SCC, n = 39 [50.6 %]), large cell carcinoma (LCLC, n = 7 [9.1 %]), adenosquamous cell carcinoma (ASC, n = 4 [5.2 %]), undifferentiated (n = 24 [31.2 %]), and others (n = 3 [3.9 %]).

The proportions of each *EGFR* mutation in our study patients treated with EGFR-TKIs were as follows: ADC patients: 19 del, 49.8 % (n = 761/1529), L858R, 44.8 % (n = 685/ 1529), and others, 5.4 % (n = 83/1529); non-ADC patients: 19 del, 45.5 % (n = 30/66), L858R, 48.5 % (n = 32/66), and others, 6.1 % (n = 4/66).

The demographic data of *EGFR*-mutated ADC and non-ADC patients are shown in Table 1. The characteristics of the *EGFR*-mutated ADC patients showed that more females than males were included in the non-ADC cohort (Fisher's exact test; $P < 0.001$). Non-ADC patients were more likely to have MPE and distant metastasis than ADC patients ($P = 0.071$ and $P = 0.022$, respectively). The patient identification flowcharts are illustrated in Fig. 1.

3.2. Comparison of the overall survival and clinical response

The *EGFR*-mutated ADC patients were more likely to have a longer median OS than the non-ADC patients [hazard ratio (HR) 1.3 (95 % CI, 0.97–1.8, $P = 0.072$), 29.5 months (95 % CI, 27.9–31.1 months) versus 19.5 months (95 % CI, 10.8–28.2 months) ($P = 0.068$)] (Fig. 2A). For patients receiving EGFR-TKI therapy, there was no significant difference in the median OS between *EGFR*-positive ADC and non-ADC patients [HR 1.1 (95 % CI, 0.8–1.6, $P = 0.468$), 29.5 months (95 % CI, 27.8–31.2 months) versus 25.5 months (95 % CI, 8.1–42.9 months) ($P = 0.462$)] (Fig. 2B). In addition, among *EGFR*-positive non-ADC patients, the median OS for patients receiving EGFR-TKI treatment was significantly longer than that of patients who did not receive the treatment [HR 4.5 (95 % CI, 2.1–9.8, $P < 0.001$), 25.5 months (95 % CI, 8.1–42.9 months) versus 7.5 months (95 % CI, 3.4–11.6 months) ($P < 0.001$)] (Fig. 2C).

Although no significant difference in OS was observed between ADC patients with 19 del and those with L858R mutations (HR 1.0 [95 % CI, 0.9–1.2, $P = 0.945$], 29.5 months [95 % CI 27.1–31.9 months] and 31.5 months [95 % CI 29.1–33.9 months], $P = 0.944$), the median OS for *EGFR*-mutated non-ADC patients with 19 del was significantly longer than that of patients with the L858R mutation (HR 3.2 [95 % CI 1.5–6.9, $P = 0.004$], 19 del was not reached, and L858R was 15.5 months [95 % CI 6.6–24.4 months], $P = 0.002$) (Fig. 3A, B).

Among the *EGFR*-mutated non-ADC NSCLC patients treated with first-generation EGFR-TKIs (regardless of the treatment line), the CR was 6.1 %, PR was 45.5 %, SD was 18.2 %, and PD was 19.7 %.

3.3. Clinical characteristics and treatment efficacy

To investigate the clinical characteristics influencing the efficacy of EGFR-TKIs in *EGFR*-mutated non-ADC NSCLC patients, the patients who received the EGFR-TKI therapy were divided into two groups on the

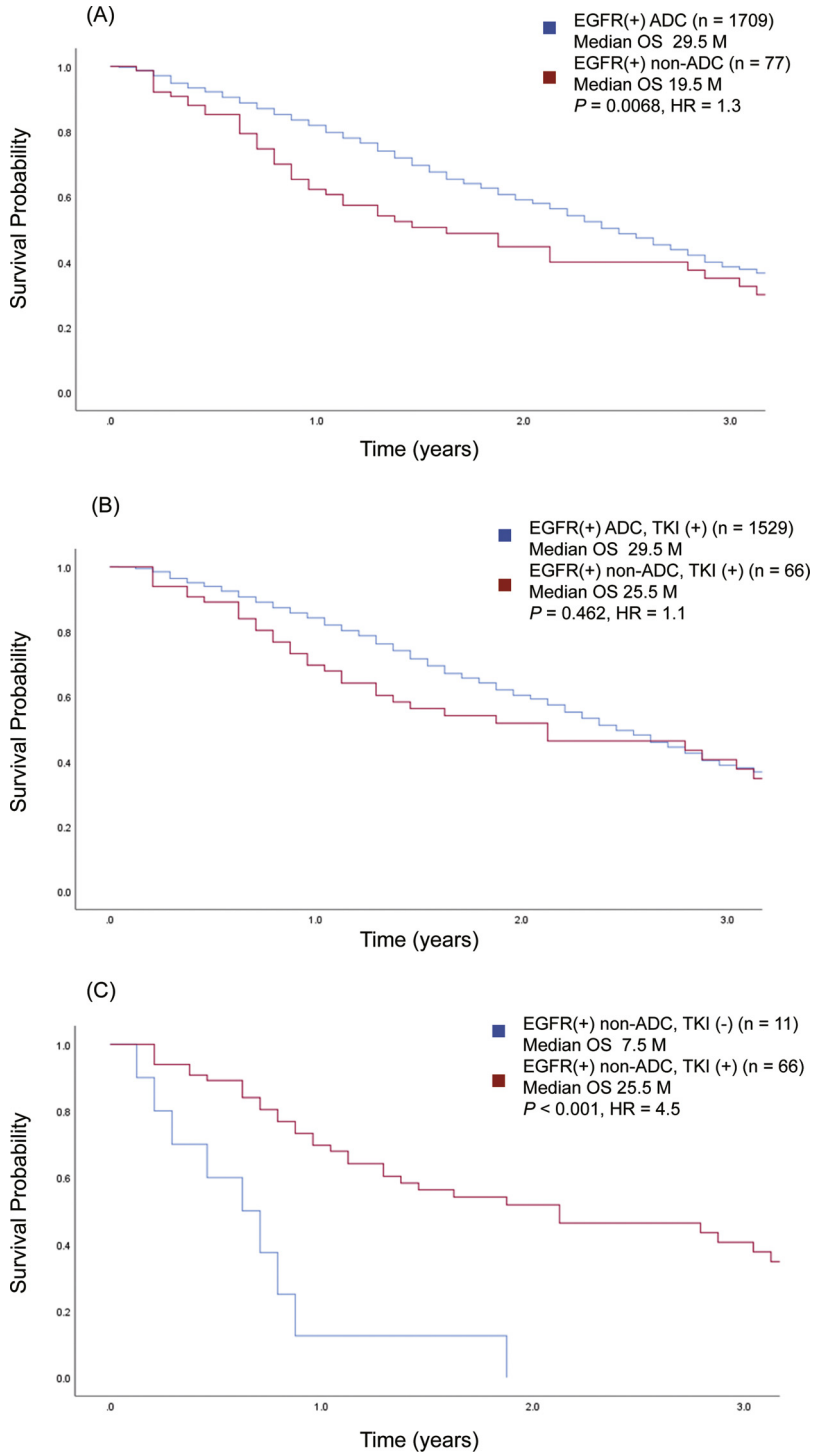

Fig. 2. (A) Overall survival curves for *EGFR*-mutated adenocarcinoma and non-adenocarcinoma. (B) Overall survival curves for *EGFR*-mutated adenocarcinoma treated with EGFR-TKI and *EGFR*-mutated non-adenocarcinoma treated with EGFR-TKI. (C) Overall survival curves for *EGFR*-mutated non-adenocarcinoma treated with EGFR-TKI and not treated with EGFR-TKI.
Abbreviations: EGFR, epidermal growth factor receptor; OS, overall survival; ADC, adenocarcinoma; TKI, tyrosine kinase inhibitor; M = months; P = probability; n = number.

basis of their response: the "response group" was defined as patients whose tumor responded to the first use of EGFR-TKI (regardless of treatment line) as a CR and a PR, and the "non-response group" was defined as patients who had achieved SD and PD. There was no significant difference in clinical characteristics between the "response group" and the "non-response group" (Table 2).

Moreover, there was no significant difference in patient characteristics between 19 del-positive and L858R-positive mutations in non-ADC patients (Table 3).

4. Discussion

The efficacy of EGFR-TKIs in non-ADC remains controversial because the number of non-ADC cases harboring *EGFR* mutations is

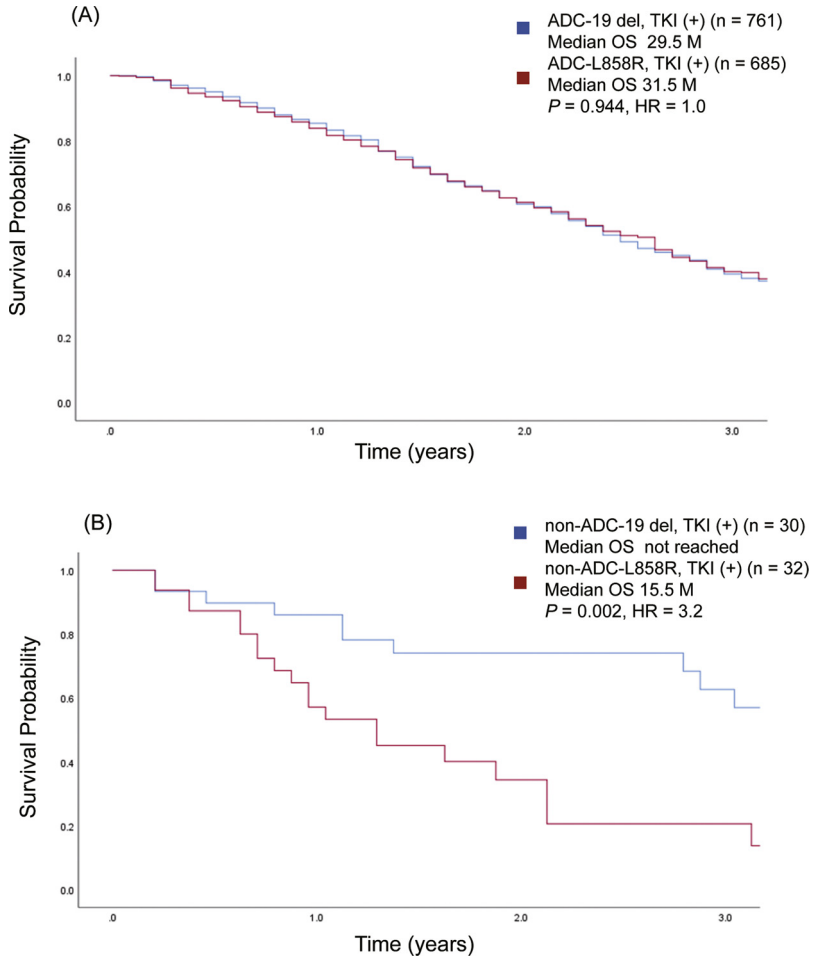

Fig. 3. (A) Overall survival curves for *EGFR*-mutated adenocarcinoma, with exon 19 deletion and exon 21 L858R mutations, treated with EGFR-TKI. (B) Overall survival curves for *EGFR*-mutated non-adenocarcinoma, with exon 19 deletion and exon 21 L858R mutations, treated with EGFR-TKI.
Abbreviations: EGFR, epidermal growth factor receptor; OS, overall survival; ADC, adenocarcinoma; 19 del, exon 19 deletion; L858R, exon 21 L858R; TKI, tyrosine kinase inhibitor; M = months; P = probability; n = number.

relatively smaller than of ADC cases harboring these mutations. Previous studies had a small sample size, and they assessed the efficacy by response rate (RR) and progression free survival, which were likely affected by investigator bias. The current study had a large sample size and a long follow-up period for OS. Moreover, we compared the differences between ADC and non-ADC, making the outcome more robust in that a lot of data and evidence is available on ADC.

For example, previous studies on ADC included more women than men in the non-ADC group [10–12], consistent with the current study (Table 1). Furthermore, for the first time, our study shows that *EGFR*-mutated non-ADC patients are more likely to have MPE and distant metastasis. ADC seems to be most commonly associated with MPE, which typically occurs in peripheral lesions [13,14]. However, it is known that the probability of MPE is also higher in LCLC, NSCLC NOS (not otherwise specified), and undifferentiated cases [15]. *EGFR*-mutated ADC patients with MPE had a higher rate of L858R mutation, which may play a role in the development of MPE [16].

Regarding distant metastasis, some studies have shown that the most frequent metastatic site of NSCLC is the bone, followed by the lung, brain, liver, and adrenal glands, and the most common combinations for two-site metastasis for SCC and LCLC were the bone and liver. On the other hand, lung and brain metastasis occurs more in *EGFR*-mutated NSCLC patients than in *EGFR*-wild type patients [17–20]. In any case, several studies have reported that liver metastasis has a poorer prognosis than other metastatic patterns [21,22]. In addition, liver metastasis may be related to exon 21 L858R [23].

The median OS for *EGFR*-mutated ADC patients treated with EGFR-TKI is known to be 21.6–34.8 months [2,24–29]. In this study, the median OS for such patients was similar (29.5 months). The RR and median OS for *EGFR*-mutated non-ADC patients treated with EGFR-TKIs were reported to be inferior, at 25 %–32 % and 14.6 months, respectively [6,7,30]; in the present study, the RR for first use of EGFR-TKI was 51.6 % and the median OS was 25.5 months. Furthermore, the median OS for *EGFR*-mutated non-ADC patients with 19 del (not reached) was significantly longer than that for patients with the L858R mutation (15.5 months).

This study shows that: 1) *EGFR*-mutated non-ADC patients are more likely to have MPE and distant metastasis. 2) *EGFR*-mutated non-ADC patients with the 19 del mutation can obtain clinical benefit from first-generation EGFR-TKI treatment.

Patients with L858R mutations will have a longer OS if administered first-generation EGFR-TKIs than if they do not receive them, but this OS will still be shorter than that of patents with the 19 del mutation (Fig. 3B). The efficacy of first-generation EGFR-TKIs had nothing to do with the type of *EGFR* mutation (Table 2). Furthermore, there was no significant difference in patient characteristics between non-ADC patients who either had 19 del or L858R mutation (Table 3). This indicates that patients with L858R mutations have a poor prognosis regardless of the efficacy of EGFR-TKIs or patient characteristics. These results are supported by preclinical studies that have demonstrated that 19 del and L858R have distinct biological properties that may affect the efficacy of EGFR-TKIs [31].

Table 2
Comparison of patient characteristics in EGFR-mutated non-adenocarcinoma between the response and non-response groups for treatment with first-generation EGFR-TKIs.

Characteristics	CR + PR (n = 34)	SD + PD (n = 25)	P value
Age (yr)			0.633
Median (range)	67.5 (32–84)	70.0 (49–88)	
Gender			0.608
Male	18 (52.9 %)	15 (60 %)	
Female	16 (47.1 %)	10 (40 %)	
Smoking history			0.122
Never	19 (55.9 %)	12 (48 %)	
Former	14 (41.2 %)	8 (32 %)	
Current	1 (2.9 %)	5 (20 %)	
PS (ECOG)			0.841
0,1,2	30 (88.2 %)	25 (100 %)	
3,4	4 (11.8 %)	0 (0%)	
Malignant pleural effusion			1
yes	26 (76.5 %)	20 (80 %)	
no	8 (23.5 %)	5 (20 %)	
Distant metastasis			0.494
yes	27 (79.4 %)	22 (88 %)	
no	7 (20.6 %)	3 (12 %)	
Lung metastasis			0.493
yes	6 (17.6 %)	4 (16 %)	
no	28 (82.4 %)	21 (84 %)	
Liver metastasis			0.191
yes	4 (11.8 %)	4 (16 %)	
no	30 (88.2 %)	21 (84 %)	
Bone metastasis			0.484
yes	44.1 (45.1 %)	12 (48 %)	
no	55.9 (54.9 %)	13 (52 %)	
Brain metastasis			0.258
yes	10 (29.4 %)	5 (20 %)	
no	24 (70.6 %)	20 (80 %)	
Adrenal metastasis			0.371
yes	2 (5.9 %)	4 (16 %)	
no	32 (94.1 %)	21 (84 %)	
Types of EGFR mutation			0.511
19 del	17 (50 %)	9 (36 %)	
L858R	15 (44.1 %)	15 (60 %)	
Others	2 (5.9 %)	1 (4%)	

Abbreviations: EGFR, epidermal growth factor receptor; yr, year; PS, performance status; 19 del, exon 19 deletion mutation; L858R, exon 21 L858R mutation; Adeno, adenocarcinoma.

Table 3
Comparison of patients characteristics between EGFR-mutated non-adenocarcinoma patients with exon 19 deletion and those with exon 21 L858R mutation.

Characteristics	19 del (n = 30)	L858R (n = 32)	P value
Age (yr)			0.156
Median (range)	68.5 (32–82)	71.5 (49–88)	
Gender			0.317
Male	19 (63.3 %)	16 (50 %)	
Female	11 (36.7 %)	16 (50 %)	
Smoking history			0.611
Never	14 (46.7 %)	19 (59.4 %)	
Former	13 (43.3 %)	10 (31.3 %)	
Current	3 (10 %)	3 (9.4 %)	
PS (ECOG)			0.613
0,1,2	29 (96.7 %)	29 (90.6 %)	
3,4	1 (3.3 %)	3 (9.4 %)	
Malignant pleural effusion			0.537
yes	5 (16.7 %)	8 (25 %)	
no	25 (83.3 %)	24 (75 %)	
Distant metastasis			0.502
yes	24 (80 %)	28 (87.5 %)	
no	6 (20 %)	4 (12.5 %)	
Lung metastasis			1
yes	5 (16.7 %)	6 (18.8 %)	
no	25 (83.3 %)	26 (81.3 %)	
Liver metastasis			0.511
yes	4 (13.3 %)	7 (21.9 %)	
no	26 (86.7 %)	25 (78.1 %)	
Bone metastasis			0.446
yes	13 (43.3 %)	18 (56.3 %)	
no	17 (56.7 %)	14 (43.8 %)	
Brain metastasis			0.775
yes	7 (23.3 %)	9 (28.1 %)	
no	23 (76.7 %)	23 (71.9 %)	
Adrenal metastasis			0.672
yes	2 (6.7 %)	4 (12.5 %)	
no	28 (93.3 %)	28 (87.5 %)	

Abbreviations: yr, year; PS, performance status; 19 del, exon 19 deletion mutation; L858R, exon 21 L858R mutation.

A major limitation of this study was that data were available only for gefitinib and erlotinib (which are first-generation EGFR-TKIs). Some patients may have been treated with afatinib (a second-generation EGFR-TKI) in this study, but we could not evaluate the efficacy of afatinib because the related data were input as “others treatments.” This study also had several minor limitations, such as it being a retrospective study and having no access to the details of treatment lines and laboratory data for each patient.

Recently, osimertinib (a third-generation EGFR-TKI) has been approved as a first-line treatment for *EGFR*-mutated advanced NSCLC [32]. However, patients with L858R mutations treated with osimertinib did not exhibit significantly better OS than patients treated with first-generation EGFR-TKIs [33].

It is known that afatinib might not improve the OS of *EGFR* L858R-positive NSCLC patients, whereas dacomitinib (a second-generation EGFR-TKI) does so [34–36]. Previous studies have claimed that patients with L858R mutations have more non-classical mutations (compound mutations) than those with 19 del, which could be the reason for the L858R mutation being associated with a poor clinical outcome [37]. Second-generation EGFR-TKIs are known to be more effective for patients with non-classical mutations lacking 19 del or L858R [38,39]. We did not estimate the ratio of compound mutations; however, treatment with second-generation EGFR-TKIs, especially dacomitinib, may be more effective for patients with L858R mutations.

Recent trials, such as ATLANTIC and IMpower150, showed that some EGFR mutant lung cancers respond to immune-checkpoint inhibitors (ICIs) [40,41]. Specifically, 19 del tumors had a worse outcome, whereas L858R tumors had RR and OS similar to those for an EGFR-wild type lung cancer population [42].

Our study also shows that *EGFR*-mutated non-ADC patients are likely to have MPE and distant metastasis. Given that L858R may be related to MPE and liver metastasis, we can suggest adding an angiogenesis inhibitor, such as ramucirumab, to EGFR-TKIs for *EGFR* L858R positive non-ADC patients [43,44].

Overall, *EGFR*-mutated non-ADC patients were more likely to have MPE and distant metastasis, including liver metastasis, which may be related to L858R mutations.

Both ADC and *EGFR* del19-positive non-ADC patients can obtain clinical benefit from EGFR-TKIs; however, *EGFR* L858R-positive non-ADC patients may not have the same OS extension. Therefore, we suggest using another treatment for these patients besides the conventional treatment, for example, using second-generation EGFR-TKIs, ICIs, or adding an angiogenesis inhibitor. Clinical trials should be undertaken to evaluate the efficacy of these treatments for *EGFR* L858R-positive non-ADC patients.

Authorship contributions

Conception and design of study: K.Kobayashi, K.S., and Y.S;

Acquisition of data: K.Kobayashi, K.S., K.F., Y.S., I.S., T.S., K.Takayama, A.U., I.S., K.Kiura, K.Takahashi, N.Y., Y.T., E.M., M.O., and I.Y.;

Analysis and/or interpretation of data: K.Kobayashi, Y.S., and E.M.

Drafting the manuscript: K.Kobayashi;

Revising the manuscript critically for important intellectual content: K.Kobayashi, K.S., and Y.S.

Approval of the version of the manuscript to be published (the names of all authors must be listed): K.Kobayashi, K.S., K.F., Y.S., I.S., T.S., K.Takayama, A.U., I.S., K.Kiura, K.Takahashi, N.Y., Y.T., E.M., M.O., and I.Y.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

All the authors declare that they have no conflict of interest related to this study.

Acknowledgments

The authors wish to thank all the contributors at the participating institutions. The Japanese Joint Committee of Lung Cancer Registry and this study were supported by The Japan Lung Cancer Society, The Japanese Respiratory Society, and The Japan Society for Respiratory Endoscopy. We would like to thank Editage (www.editage.com) for English language editing.

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