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The impact of epidermal growth factor receptor mutations on patterns of disease recurrence after chemoradiotherapy for locally advanced non–small cell lung cancer: a literature review and pooled analysis

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ABSTRACT

The purpose of this review was to evaluate the impact of epidermal growth factor receptor (*EGFR*) mutation status on disease recurrence in patients treated with chemoradiotherapy (CRT) for locally advanced non–small cell lung cancer (NSCLC). A literature search was conducted and a total of three studies were analyzed. There was no significant difference in the objective response rate between the *EGFR* mutation group and the *EGFR* wild-type group (odds ratios [OR] 1.46, 95% CI, 0.79–2.70, $P = 0.228$), and there was no significant difference in the incidence of disease recurrence (OR 1.37, 95% CI, 0.68–2.75, $P = 0.379$) between the two groups. There were significant difference in the incidence of local/locoregional progression (LP) (OR 0.35, 95% CI, 0.18–0.71, $P = 0.003$) and distant progression (DP) (OR 2.97, 95% CI, 1.59–5.54, $P < 0.001$). Brain metastasis (BM) was one of the main recurrence patterns of DP, and the incidence was significantly higher in the *EGFR* mutant group (OR 2.75, 95% CI, 1.43–5.31, $P = 0.003$). There were no statistically significant heterogeneities in these pooled analyses. The patterns of recurrence after CRT for locally advanced NSCLC were different according to *EGFR* mutation status. LP after CRT in patients with *EGFR* mutation was less frequent, but the high incidence of DP, especially BM, continued to be the major problem. On the other hand, LP continued to be the major problem in *EGFR* wild-type patients. In multimodality treatment for inoperable locally advanced NSCLC, we may need to consider different treatment strategies according to *EGFR* mutation status.

INTRODUCTION

Lung cancer is the most frequently diagnosed cancer in the world, and it accounts for 13% of all cancers diagnosed. It is estimated that lung cancer contributes to more than 1.6 million deaths each year [1]. Non–small cell lung cancer (NSCLC) accounts for ~90% of new lung cancer diagnoses, and approximately one-third of NSCLC patients present with locally advanced disease [2–4]. Concurrent chemoradiotherapy (CCRT) is considered to be the standard therapy for locally advanced and inoperable NSCLC patients [5], and sequential chemoradiotherapy (CRT) is considered to be one of the treatment options for elderly patients or those with poor performance status [6, 7].

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein and a member of the erbB receptor tyrosine kinase family, and it is commonly overexpressed in NSCLC [8, 9]. Following ligand-binding, EGFR receptors homo- and heterodimerize and promote autophosphorylation of the intracellular tyrosine

kinase domain, and thus initiate a molecular cascade of events involved in growth, and cell proliferation, differentiation and survival [9–12]. It has been reported that *EGFR* mutations occur more frequently in Asian patients compared with European or North American patients, with mutation rates of ~30% and ~10%, respectively [13–15].

NSCLC cell lines with *EGFR* mutations have been reported to be more sensitive to radiation in an *in vitro* study [16]. It has also been reported that intracranial progression-free survival (or response rate) after cranial radiotherapy (RT) for brain metastases (BM) from NSCLC is favorable in patients with *EGFR* mutations [17–19]. A difference in the effectiveness of definitive CRT for locally advanced NSCLC according to *EGFR* mutation status in patients has not yet been established. The purpose of this study was to evaluate any association between *EGFR* mutation status and disease recurrence after CRT for NSCLC.

METHOD

A literature search, via PubMed and EMBASE, using the following terms and keywords: radiation therapy, radiotherapy, lung cancer, non–small cell lung cancer, non–small cell lung carcinoma, NSCLC, epidermal growth factor, EGFR, and a combination of these terms. The last research was conducted on 29 February 2016.

Data collection

For eligibility, studies were required to meet the following criteria: (i) studies which evaluated the effect of *EGFR* mutation status on the clinical outcome of locally advanced NSCLC; (ii) studies involving multimodality treatment including thoracic radiation therapy (RT); (iii) studies published in English, regardless of publication time; (iv) original papers containing a threshold amount of data. Studies failing to meet the eligibility criteria were excluded. Our focus was to evaluate the incidence of disease recurrence (DR) (local/locoregional progression [LP], distant progression [DP], BM) according to *EGFR* mutation status. Differences in patient characteristics (gender, smoking history) and tumor characteristics (clinical stage, clinical T stage and N stage), objective response rate (ORR), progression-free survival (PFS)/relapse-free survival (RFS), and overall survival (OS) were also compared in relation to *EGFR* mutation status. In this analysis, objective response was defined as complete response or partial tumor response according to the Response Evaluation Criteria for Solid Tumors (RECIST).

Statistical analysis

For each study, baseline characteristics, ORR and DR, were compared using Fisher's exact test. The results of studies were reported as pooled odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). The Mantel–Haenszel method was used to estimate the pooled OR and its 95% CI in a fixed effect model. The homogeneity of the studies was tested by Q statistics and I^2 statistic (I^2 = 0–50% for no or moderate heterogeneity; I^2 > 50%, significant heterogeneity), which are quantitative measures of inconsistency across the studies [20]. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, The R Foundation for Statistical Computing) [21]. A *P*-value of <0.05 was inferred to be statistically significant.

RESULTS

A total of seven retrospective studies were identified [22–28]. RT was used as the only preoperative therapy in one study, which was thus excluded from further analysis [25]. One paper was in Chinese, and that study was also excluded from further analysis, based on the eligibility criteria [23]. One study included both patients who had received definitive CRT and others who had received perioperative CRT [22]. Evaluation of DR after CRT was difficult, and that study was also excluded. A fourth study included patients treated with RT or CRT [24]. It was difficult to evaluate the endpoints of this analysis separately for the RT and the CRT cohorts, and in light of the differences in treatment outcomes between RT and CRT [29], that study was also excluded. The data from the remaining three retrospective studies were evaluated in this article [26–28].

Patient, tumor and treatment characteristics

Patient, tumor and treatment characteristics of included studies according to *EGFR* mutation status are summarized in Table 1. Two studies [27, 28] contained enough data to compare smoking history, clinical T stage and clinical N stage, and these studies were included in our pooled analysis.

There was be no significant difference in the median patient age between the two groups. The median irradiated dose of all patients who underwent definitive CRT was 60 Gy, and there was no difference between that for the *EGFR* mutant group and that for the *EGFR*-wild type group. One study included both patients who underwent CCRT (84%) and others who underwent sequential CRT (16%) [27]. The proportion of patients who underwent CCRT was not statistically different between the *EGFR* mutant group (76%) and the *EGFR* wild-type group (85%) ($P = 0.206$). The other studies only included patients who underwent CCRT [26, 28]. Using Fisher's exact test, there was a significant difference between the gender ratio for the *EGFR* mutant group and the *EGFR* wild-type group in two of the studies [27, 28]. There was also a significant difference in the between the smoking history of the two groups in all of the evaluated studies [27, 28]. In the pooled analysis, females (OR 4.87, 95% CI, 2.81–8.45, $P < 0.001$) and never-smokers (OR 12.43, 95% CI, 6.45–23.95, $P < 0.001$) were more frequently observed in the *EGFR* mutant group than in the *EGFR* wild-type group (Fig. 1).

Based on Fisher's exact test, there were no significant differences in the clinical stage (Stage II–IIIA vs IIIB) or N stage (cN0–2 vs cN3) between the two groups. However, there were significant differences in the comparison of clinical T stage (cT1–2 vs cT3–4) between the two groups in both evaluated studies [27, 28]. In the pooled analysis, there was no significant difference in the clinical stage (OR 0.90, 95% CI, 0.53–1.51, $P = 0.683$) between the two groups. The patients with advanced T stage were less frequently observed in the *EGFR* mutant group compared with in the *EGFR* wild-type group (OR 0.14, 95% CI, 0.06–0.33, $P < 0.001$). The patients with advanced N stage tended to be more frequently observed

Table 1. Summary of patient, tumor and treatment characteristics

Study	*EGFR* mutation status	Akamatsu *et al.* (2014) [26]	Yagishita *et al.* (2015) [27]	Tanaka *et al.* (2015) [28]
Total no. of Pts		44	198	104
Histology		Adc	nonsquamous NSCLC	Adc
Concurrent administration of chemotherapy (%)		44 (100)	166 (84)	104 (100)
EGFR mutation (%)				
	EGFR-m	13 (30)	34 (17)	29 (28)
	EGFR-w	31 (70)	164 (83)	75 (72)
Median age, years (range)				
	EGFR-m	68	62 (46–75)	62 (51–77)
	EGFR-w	64	60 (32–76)	62 (40–74)
Median RT dose, Gy (range)				
	EGFR-m	60 (60–74)	60 (60–72)	60 (60–66)
Concurrent CRT (%)				
	EGFR-m	13 (100)	26 (76)	29 (100)
	EGFR-w	31 (100)	140 (85)	75 (100)
	P-value	>0.999	0.206	>0.999
Gender, no. of females (%)				
	EGFR-m	5 (38)	18 (54)	20 (69)
	EGFR-w	7 (23)	28 (17)	20 (27)
	P-value	0.295	**<0.001**	**<0.001**
Never-smoker (%)				
	EGFR-m	NA	20 (59)	18 (62)
	EGFR-w	NA	18 (11)	8 (11)
	P-value		**<0.001**	**<0.001**
Clinical Stage IIIB (%)				
	EGFR-m	4 (31)	14 (41)	16 (55)
	EGFR-w	9 (69)	78 (48)	41 (55)
	P-value	0.321	0.573	>0.999
T3–4 (%)				
	EGFR-m	NA	1 (3)	6 (21)
	EGFR-w	NA	67 (41)	37 (49)
	P-value		**<0.001**	**0.008**

Continued

Table 1. Continued

Study	*EGFR* mutation status	Akamatsu *et al.* (2014) [26]	Yagishita *et al.* (2015) [27]	Tanaka *et al.* (2015) [28]
N3 (%)	*EGFR*-m	NA	13 (38)	14 (48)
	EGFR-w	NA	48 (29)	27 (36)
	P-value		0.313	0.662

EGFR = epidermal growth factor receptor, Pts = patients, *EGFR*-m = *EGFR* mutant group; *EGFR*-w = *EGFR* wild-type group, Adc = adenocarcinoma; NSCLC = non–small cell lung cancer, CRT = chemoradiotherapy, RT = radiation therapy, *P*-value: *P*-value of Fisher's exact test, NA = not available.

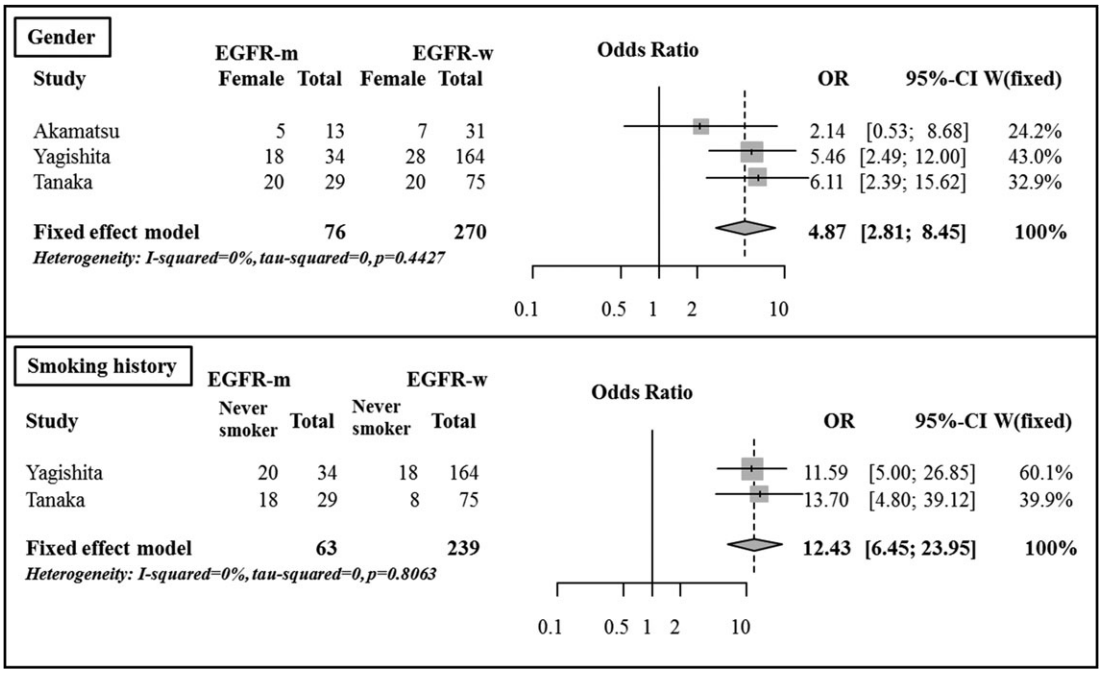

Fig. 1. Comparison of patient characteristics between the *EGFR* mutant group and the *EGFR* wild-type group.

in the *EGFR* mutant group, but the difference was not statistically significant (OR 1.57, 95% CI, 0.88–2.78, $P = 0.126$) (Fig. 2).

Objective response rate

Although there were slight differences in the versions between the studies, ORRs were evaluated using RECIST criteria in all of the studies. RECIST verison 1.0 was used in one study [26], and version 1.1 was used in two studies [27, 28]. ORRs after CRT according to EGFR mutation status are summarized in Table 2. Based on Fisher's exact test, there were no significant differences in the comparison of ORR between the *EGFR* mutant group and the *EGFR* wild-type group. There were no significant differences in the ORR between the two groups (OR 1.46, 95% CI, 0.79–2.70, $P = 0.228$) (Fig. 3).

Disease recurrence

The rates of DR after definitive CRT are summarized in Table 3. There were no significant differences between the rates of DR for the *EGFR* mutant and the *EGFR* wild-type groups, using Fisher's exact tests and the pooled analysis (OR 1.37, 95% CI, 0.68–2.75, $P = 0.379$) (Fig. 4).

Local/locoregional progression

There was a significant difference between the groups with respect to the incidence of LP for one study, using Fisher's exact test ($P = 0.039$); the rate of LP was less frequent in the *EGFR* mutant group (17% vs 35%). In the pooled analysis, LP was shown to be significantly less frequent in the *EGFR* mutant group compared with the *EGFR* wild-type group (OR 0.35, 95% CI, 0.18–0.71, $P = 0.003$) (Fig. 5).

Distant progression

There were significant differences in the incidences of DP between the two groups in one study, based on Fisher's exact test [28]. DP was reported to be more frequent in the *EGFR* mutant group (76% vs 40%, $P = 0.002$) [28]. In the pooled analysis, DP was shown to be significantly more frequent in the *EGFR* mutant group compared with in th *EGFR* wild-type group (OR 2.97, 95% CI, 1.59–5.54,

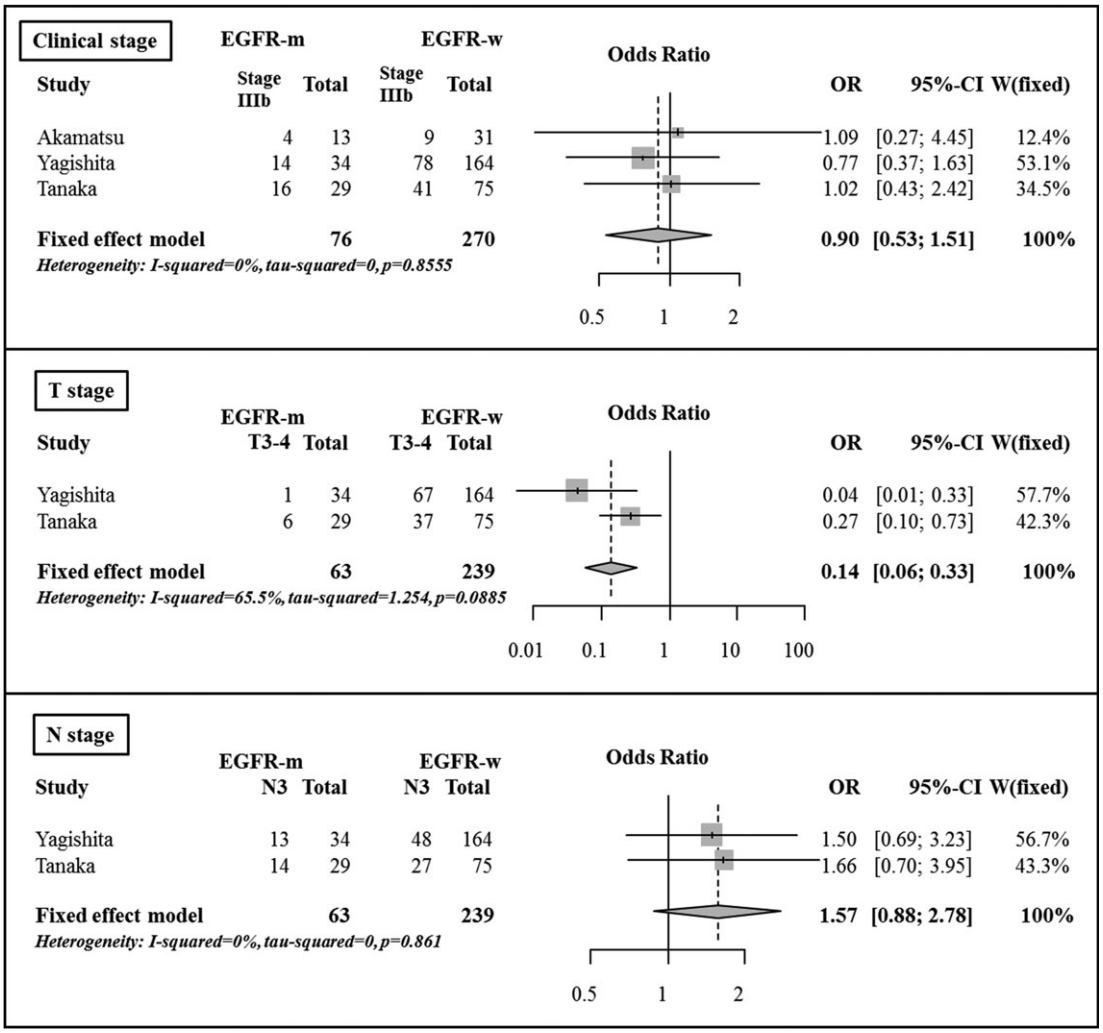

Fig. 2. Comparison of tumor characteristics between the *EGFR* mutant group and the *EGFR* wild-type group.

Table 2. Objective response rate

	EGFR mutation status	Akamatsu *et al.* (2014) [26]	Yagishita *et al.* (2015) [27][a]	Tanaka *et al.* (2015) [28]
Total no. of evaluated Pts		44	184	104
EGFR mutant (%)		13 (30)	29 (16)	29 (28)
Objective response (%)				
	EGFR-m	10 (77)	23 (79)	21 (72)
	EGFR-w	13 (43)	118 (76)	54 (72)
	P-value	0.185	0.678	>0.999

[a]Patients who were enrolled in the JCOG 0402 trial, had received RT at a total dose of <50 Gy, or who received epidermal growth factor receptor–tyrosine kinase inhibitor therapy before CRT were excluded. *EGFR* = epidermal growth factor receptor, Pts = patients, *EGFR*-m = *EGFR* mutant group, *EGFR*-w = *EGFR* wild-type group, *P*-value = *P*-value of Fisher's exact test.

$P < 0.001$), and the incidence of DP was significantly higher in the *EGFR* mutant group compared with in the *EGFR* wild-type group (Fig. 6).

Brain metastases

For the BM evaluation, three studies contained enough data to be included [26–28]. There were significant differences between the

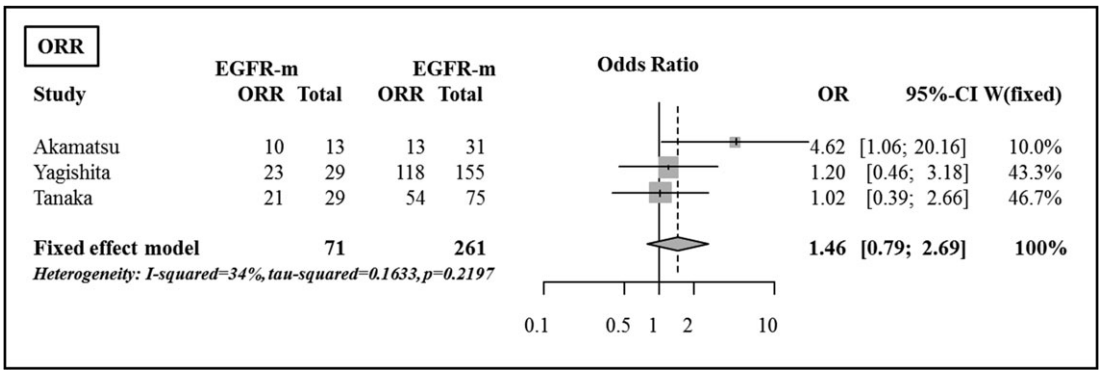

Fig. 3. Comparison of objective response rate between the *EGFR* mutant group and the *EGFR* wild-type group.

Table 3. Disease recurrence

	EGFR mutation status	Akamatsu *et al.* (2014) [26]	Yagishita *et al.* (2015) [27][a]	Tanaka *et al.* (2015) [28]
Total no. of evaluated Pts		44	184	104
No. of Pts (%)				
	EGFR-m	13 (30)	29 (16)	29 (28)
	EGFR-w	31 (70)	155 (84)	24 (83)
Disease recurrence (%)				
	EGFR-m	10 (77)	25 (86)	24 (83)
	EGFR-w	26 (84)	129 (83)	53 (71)
	P-value	0.676	0.503	0.318
Local/locoregional progression (%)				
	EGFR-m	2 (15)	5 (17)	4 (14)
	EGFR-w	10 (32)	54 (35)	26 (35)
	P-value	0.459	**0.039**	0.052
Distant progression (%)				
	EGFR-m	9 (69)	24 (83)	22 (76)
	EGFR-w	18 (58)	102 (66)	30 (40)
	P-value	0.735	0.435	**0.002**
Brain metastases (%)				
	EGFR-m	6 (46)	4 (14)	10 (35)
	EGFR-w	4 (13)	15 (10)	11 (15)
	P-value	**0.043**	0.748	**0.031**

[a]Patients who were enrolled in the JCOG 0402 trial, had received RT at a total dose of <50 Gy, or who received epidermal growth factor receptor–tyrosine kinase inhibitor therapy before CRT were excluded. *EGFR* = epidermal growth factor receptor, Pts = patients, *EGFR*-m = *EGFR*-mutant group, *EGFR*-w = *EGFR* wild-type group, *P*-value = *P*-value of Fisher's exact test.

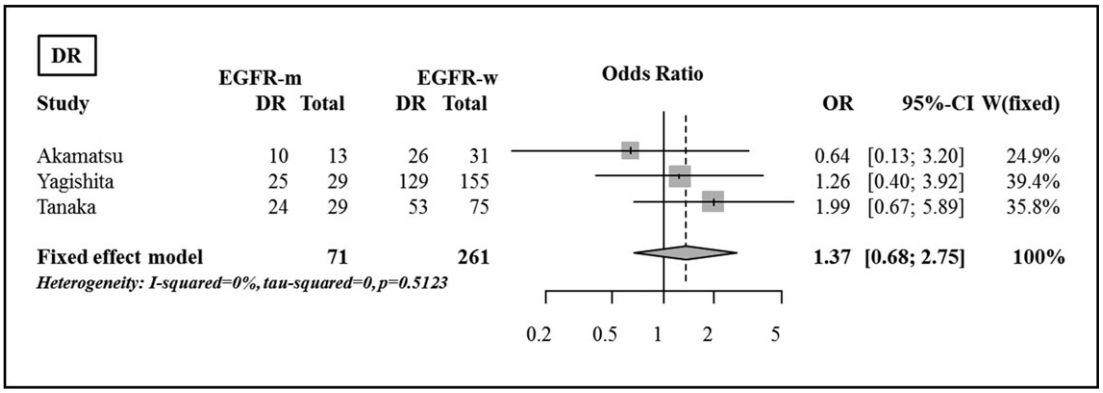

Fig. 4. Comparison of disease recurrence between the *EGFR* mutant group and the *EGFR* wild-type group.

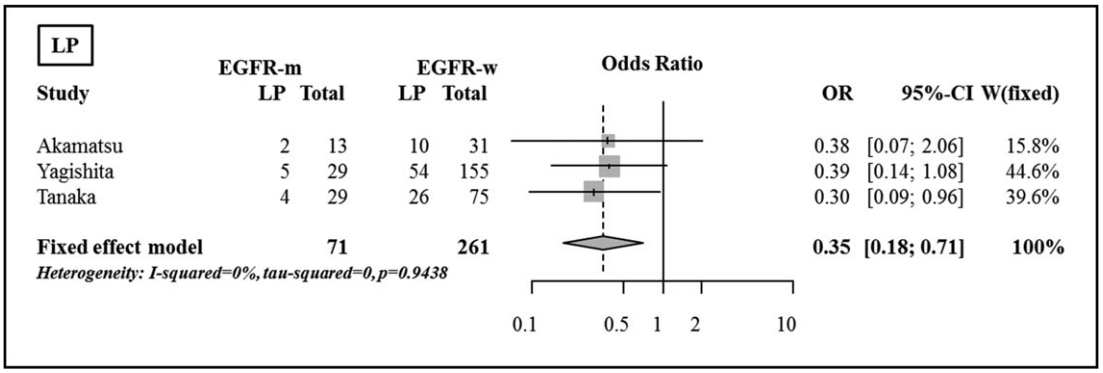

Fig. 5. Comparison of local/locoregional progression between the *EGFR* mutant group and the *EGFR* wild-type group.

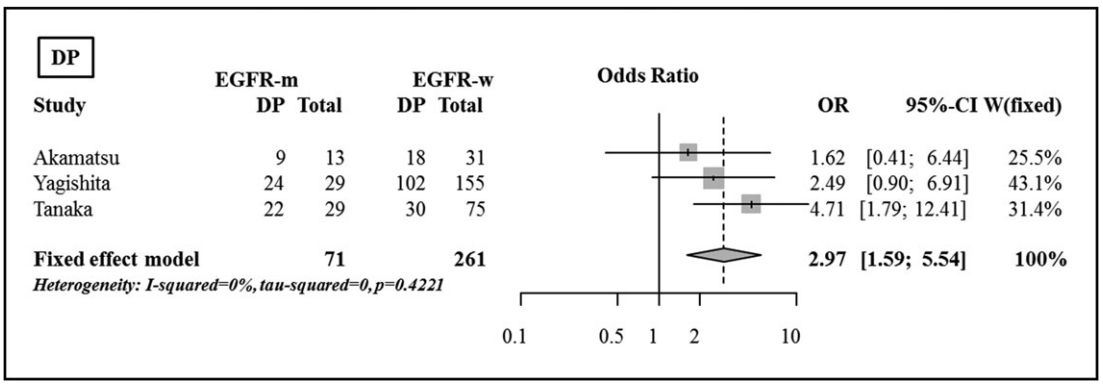

Fig. 6. Comparison of distant progression between the *EGFR* mutant group and the *EGFR* wild-type group.

two groups in the incidence of BM in two of the studies, based on Fisher's exact test [26, 28]. The incidence of BM was higher in the *EGFR* mutant group in both studies (46% vs 13%, $P = 0.043$; 35% vs 11%, $P = 0.031$). In the pooled analysis, the incidence of BM was shown to be significantly higher in the *EGFR* mutant group compared with in the *EGFR* wild-type group (OR 2.75, 95% CI, 1.43–5.31, $P = 0.003$) (Fig. 7).

Progression/relapse-free survival

The terms and definitions used for these endpoints differed between the studies. The term 'PFS' was used in two of the studies [26, 28], but 'RFS' was used in another trial [27]. Although there were slight differences in the definitions used, these endpoints were calculated from the date of initiation of CRT to detection of DR or death from any cause in the two studies [26, 27]. PFS was calculated from

the date of initiation of CCRT to either the date of recurrence or the date of last contact [28]. The reported results for RFS/PFS are summarized in Table 4. The 2-year estimated probabilities were based on Kaplan–Meier plots in one study [26]. There were no statistically significant differences in RFS/PFS between the *EGFR* mutant group and the *EGFR* wild-type group, except for in one study [28], in which the definition of PFS was different from that of the other studies.

Overall survival

Although there were slight differences in the definition, this endpoint was calculated from the initiation of CRT to the date of death from any cause in three studies [26–28]. The reported results of OS are summarized in Table 4. There were no significant differences in OS between the *EGFR* mutant group and the *EGFR* wild-type group.

DISCUSSION

In this article, we evaluated the differences between the *EGFR* mutant group and the *EGFR* wild-type group in the setting of definitive CRT for locally advanced NSCLC. Females (OR 4.94, $P < 0.001$) and never-smokers (OR 11.10, $P < 0.001$) were more frequently observed in the *EGFR* mutant group compared with in the *EGFR* wild-type group. It has been reported that *EGFR* mutation is seen more frequently in non-smoking females with adenocarcinoma, and our results were compatible with those findings [30–32].

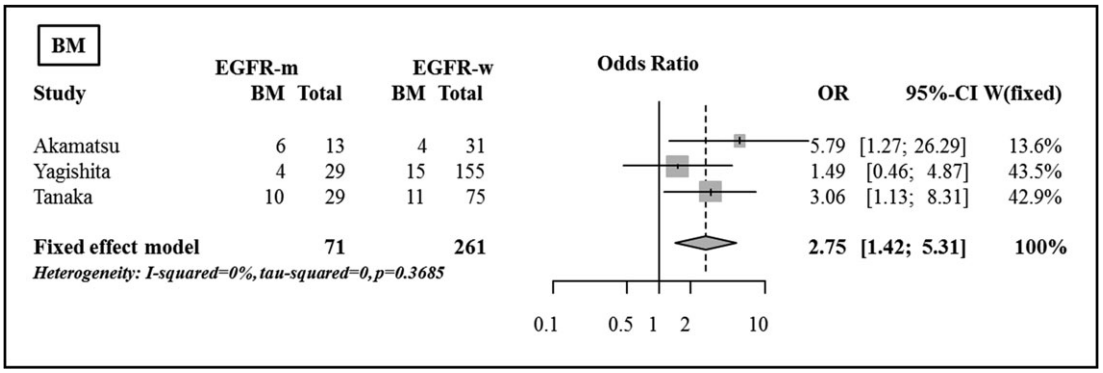

Fig. 7. Comparison of brain metastases between the *EGFR* mutant group and the *EGFR* wild-type group.

Table 4. Progression/relapse-free survival and overall survival

Study	*EGFR* mutation status	Akamatsu *et al.* (2014) [26]	Yagishita *et al.* (2015) [27][a]	Tanaka *et al.* (2015) [28]
Evaluated outcome		PFS	RFS	PFS
Median time (mo)				
	EGFR-m	9.6	12.1	9.8
	EGFR-w	13.2	10.9	16.5
2-year estimated probability				
	EGFR-m	(24)[b]	22	7.7
	EGFR-w	(29)[b]	30	28.1
	Reported *P*-value	0.78	0.545	**0.028**
Median survival time (mo)				
	EGFR-m	57	46.9	51.1
	EGFR-w	30.7	33.3	42.9
	Reported *P*-value	NA	0.158	0.637

[a]Patients who were enrolled in JCOG 0402 trial, had received RT at a total dose of <50 Gy, or who had received epidermal growth factor receptor–tyrosine kinase inhibitor therapy before CRT were excluded.
[b]The values were estimated using reported Kaplan–Meier plots. *EGFR* = epidermal growth factor receptor, PFS = progression-free survival, RFS = relapse-free survival, mo = months, *EGFR*-m = *EGFR*-mutant group, *EGFR*-w = *EGFR* wild-type group, *P*-value = *P*-value of log-rank test, NS = not statistically significant, NA = not available.

There were no significant differences in clinical stage (OR 0.90, $P = 0.683$) or N stage (OR 1.57, $P = 0.126$) between the *EGFR* mutant group and the *EGFR* wild-type group. However, patients with advanced T stage were less frequently observed in the *EGFR* mutation group (OR 0.14, $P < 0.001$).

In ORR, there was no significant difference between the *EGFR* mutant group and the *EGFR* wild-type group in the pooled analysis (OR 1.46, $P = 0.228$). Gow *et al.* reported the clinical response to whole brain radiation therapy (WBRT) for BM from lung adenocarcinoma [17]. In their analysis, the response rate was more favorable in the *EGFR* mutant group compared with in the *EGFR* wild-type group (54% vs 24%, $P = 0.045$), and administration of *EGFR* tyrosine kinase inhibitor (TKI) ($P = 0.034$) and an *EGFR* mutation ($P = 0.029$) were shown to be independent factors associated with response to WBRT. Thus, the ORR after CRT for locally advanced NSCLC and BM could be different. BM could be resistant to systemic chemotherapy due to the blood–brain barrier [33]. On the other hand, all the patients included in our analysis were administered chemotherapy. The effect of chemotherapy might contribute to minimizing the difference in response to RT in locally advanced NSCLC.

Overall, the incidence of DR did not differ between the *EGFR* mutant group and the *EGFR* wild-type group (OR 1.37, $P = 0.379$). However, the patterns of recurrence did differ between the two groups. The incidence of LP was shown to be significantly less frequent in the *EGFR* mutant group (OR 0.35, $P = 0.003$) in our pooled analysis. One possible explanation for the difference in LP is the difference in sensitivity to radiation as shown in the *in vitro* study [16]. Another possible explanation is the difference in T stage between the *EGFR* mutant group and the *EGFR* wild-type group. Patients with advanced T stage were less frequently observed in the *EGFR* mutant group compared with in the *EGFR* wild-type group. Although advanced T stage could be a risk factor for LP after CRT for NSCLC, this is still controversial [34]. Among the studies that were included in our analysis, risk factors for LP were investigated in one study [27]. Neither T stage nor diameter of the primary tumor were significant factors for time to local relapse in univariate and multivariate analysis. Schytte *et al.* investigated risk factors for LP after definitive RT for NSCLC using logistic regression analysis [34]. Gross tumor volume was the only significant factor for intrapulmonary failure ($P = 0.04$), and advanced T stage (T3/4) had borderline significance ($P = 0.06$) in their study. Although there could be a significant correlation between T stage and gross tumor volume, gross tumor volume was reported to be a risk factor for locoregional failure after CCRT for NSCLC in another study [35]. The Cox proportional hazard model was used to investigate risk factors for locoregional failure in the analysis, and $\log_{10}$ (volume) was shown to be the only significant factor for locoregional failure in multivariate analysis. These findings indicate that tumor volume is a more important factor than T stage or N stage for LP after CRT for NSCLC. Correlation between tumor volume and LP was not evaluated in the studies that were included in our analysis, and this needs further investigation. On the other hand, Yagishita *et al.* reported that timing of chemotherapy (sequential vs concurrent) was the significant factor correlated with time to local relapse in univariate analysis ($P = 0.036$), and this correlation had borderline significance in multivariate analysis ($P = 0.054$) [27]. This was compatible with the results of several randomized trials and meta-analyses [36, 37].

The incidence of DP was significantly higher in the *EGFR* mutant group (OR 2.97, $P < 0.001$) compared with in the *EGFR*-wild type group. The brain has been reported to be the site most often affected in *EGFR*-mutant patients after CRT for locally advanced NSCLC [28]. In our pooled analysis, the incidence of BM was shown to be significantly higher in the *EGFR* mutant group compared with in the *EGFR*-wild type group (OR 2.75, $P = 0.003$).

Considering these results, LP after CRT for NSCLC is less frequent in patients with *EGFR* mutations, and CRT is considered to be the effective local treatment. On the other hand, a high incidence of DP, especially BM, is still a major problem. In patients with *EGFR* mutations, the benefit of administration of TKI as adjuvant or maintenance therapy has been reported in patients with locally advanced or metastatic NSCLC [38, 39], and this could be promising in decreasing DP, including BM, after CRT. Although the considerations for prognosis of patients with BM from NSCLC had been insufficient [40, 41], the survival time after diagnosis of BM has been reported to be longer in patients with *EGFR* mutations compared with those without *EGFR* mutations. [42, 43]. In the treatment of BM, upfront cranial RT for patients has been reported to improve intracranial disease PFS and OS compared with TKI alone [44]. However, neurological adverse events are still a problem. Considering the relatively favorable prognosis of these patients, concomitant use of memantine or hippocampal sparing during WBRT would be beneficial to reduce the potentially negative effects of WBRT on cognitive function [45–48].

On the other hand, local control after CRT is far from satisfactory in patients in the *EGFR* wild-type group, and LP after CRT is still a major problem. At this time, the benefits int terms of survival or local control from dose escalation with conventionally fractionated RT above 60 Gy in unselected locally advanced NSCLC are unclear according to the results of RTOG 0617 [49]. In the trial, the irradiated dose to the normal organs was higher in the dose-escalated group (74 Gy) compared with inn the standard-dose group (60 Gy) [50, 51]. Liao *et al.* reported that the irradiated dose to the heart and lung correlated with OS after CRT for locally advanced NSCLC, and the survival of patients who were irradiated with a higher dose to these organs was unfavorable [52]. To reduce the radiation dose to normal organs, irradiation with intensity-modulated radiation therapy (IMRT) would be useful. Indeed, IMRT was reported to be associated with an improvement in the median OS and 5-year survival rate, in patients with T3 and T4 disease, compared with 3D conformal radiation therapy ($P = 0.021$) [53]. This association was also confirmed in a propensity score–matched cohort of T3 and T4 patients (hazard ratio: 0.80, 95% CI, 0.64–1.00, $P = 0.048$). Patients with *EGFR* wild-type more frequently had an advanced tumor, and IMRT might provide a survival benefit for this population.

The analyses of this article had several limitations. The studies included in our analyses were all retrospective studies and from a single institution. The policies of treatment and follow-up might vary among institutions. The differences in histology included in the studies also pose a limitation. The treatment efficacies and patterns of recurrence after CRT might be differ between the histologies of

NSCLC. The studies included in our analysis were all from Japan and most of the included patients were Asian. Difference between ethnicities could not be evaluated. Despite these limitations, our analyses contribute to understanding the effects of *EGFR* mutation status on patterns of recurrence after CRT for locally advanced NSCLC.

In conclusion, we reviewed literature that compared the outcomes according to *EGFR* mutation status after CRT for locally advanced NSCLC. In patients with *EGFR* mutation, CRT seemed to be a highly effective treatment for local control, and RT is essential in multimodality treatment. DP, especially BM, is the major problem in this population. In patients with *EGFR* wild-type, LP still remains a major problem. Patients frequently have a tumor with advanced T stage, and the application of advanced RT technique would contribute to an improved outcome by reducing the radiation dose to the normal organs in this population.

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CONFLICT OF INTEREST

There is no conflict of interest, grant or any other assistance to be disclosed for any of the authors.

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