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Original Article

Effect of Tegafur–Uracil in Resected Stage IB Lung Adenocarcinoma According to Presence or Absence of Epidermal Growth Factor Receptor Gene Mutation: A Retrospective Cohort Study

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Purpose: Tegafur–uracil (UFT) is the standard postoperative adjuvant therapy for stage IB lung adenocarcinoma (LUAD) in Japan. This study aimed to determine whether UFT is effective in stage IB LUAD with and without *epidermal growth factor receptor* (*EGFR*) mutations.

Methods: This retrospective study included 169 patients with stage IB LUAD who underwent complete resection at our department between 2010 and 2021. We investigated the clinicopathological and prognostic impact of *EGFR* mutations as well as the postoperative use of UFT.

Results: *EGFR* mutation-positive cases tended to show a higher cumulative recurrence rate than *EGFR* mutation-negative cases (p = 0.081), while overall survival was comparable between the groups (p = 0.238). In the entire cohort, UFT administration was not an independent prognostic factor in the multivariate regression analysis (p = 0.112). According to a stratification analysis, UFT administration was independently associated with favorable overall survival (p = 0.031) in *EGFR* mutation-negative cases, while it was not associated with recurrence-free survival (p = 0.991) or overall survival (p = 0.398) in *EGFR* mutation-positive cases.

Conclusion: UFT administration can improve the prognosis of *EGFR* mutation-negative LUAD but not *EGFR* mutation-positive LUAD. Thus, clinical trials of adjuvant-targeted therapy for *EGFR* mutation-positive stage IB LUAD should also be conducted in Japan.

Keywords: stage IB lung adenocarcinoma, epidermal growth factor receptor mutation, tegafur–uracil, prognosis

Introduction

Lung cancer, which is common worldwide, is associated with a high mortality rate.[1)] Although resection for localized nonsmall cell lung cancer (NSCLC) can be curative, postoperative recurrence is often fatal. Many postoperative adjuvant chemotherapy trials have been conducted worldwide to suppress recurrence by minimal

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residual disease after resection, and some drugs have been shown to be effective in suppressing recurrence. In particular, the usefulness of cisplatin-based adjuvant chemotherapy has been confirmed in several trials conducted in the 2000s, but its usefulness in stage I disease has not been confirmed.[2–5] The Cancer and Leukemia Group B (CALGB) 9633 trial investigated the usefulness of adjuvant therapy with carboplatin plus paclitaxel in stage IB (tumor diameter >3 cm) Japan Lung Cancer Research Group (JLCRG).[6] However, in this trial, adjuvant therapy was only shown to be effective for tumors of >4 cm in diameter.[7] In contrast, a JLCRG trial conducted in Japan showed the usefulness of the oral administration of tegafur–uracil (UFT) for resected T2 (tumor diameter >3 cm) N0M0 lung adenocarcinoma (LUAD).[8,9] A subsequent meta-analysis confirmed its usefulness for stage I LUAD with a tumor diameter of >2 cm to ≤3 cm.[10] Therefore, in Japan, UFT is recommended for resected stage I LUAD with a tumor diameter of >2 cm to ≤5 cm and/or the presence of pleural invasion.[11]

Comprehensive genomic profiling of NSCLC has identified various oncogenic drivers against which targeted agents have demonstrated excellent efficacy.[12] *Epidermal growth factor receptor* (*EGFR*) mutations are common oncogenic drivers of LUAD. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI), has shown excellent efficacy in metastatic LUAD with *EGFR* mutations and is recommended as a first-line treatment for this population in Japan.[13] In the ADAURA trial (ClinicalTrials.gov identifier: NCT02511106), patients with completely resected stage IB–IIIA *EGFR* mutation-positive NSCLC who received osimertinib for 3 years after adjuvant chemotherapy showed favorable disease-free survival and overall survival (OS). In the subgroup analysis of the ADAURA trial, osimertinib tended to improve OS in patients with resected stage IB NSCLC with *EGFR* mutations.[14] However, because UFT is the standard postoperative adjuvant treatment for stage IB disease in Japan, no Japanese patients were enrolled in the trial. On the other hand, although adjuvant therapy with cytotoxic anticancer agents, including UFT, has been shown to be ineffective in patients with *EGFR* mutations at various stages,[15–17] no studies have examined differences in the effects of UFT with and without *EGFR* mutations in a population composed solely of patients with stage IB disease. Therefore, the aim of this study was to characterize stage IB LUAD with *EGFR* mutations and clarify the difference in the prognostic impact of UFT in *EGFR* mutant (*EGFR*-mt) and *EGFR* wild-type (*EGFR*-wt) cases.

Materials and Methods

This study enrolled 169 patients with pathological stage IB LUAD according to the seventh edition of the tumor, node, and metastasis (TNM) classification.[11] The patients underwent radical lobectomy or bilobectomy in our department between January 2010 and December 2021. All patients underwent preoperative computed tomography (CT) and positron emission tomography, and brain metastases were evaluated using head MRI or CT. Patients who received preoperative induction therapy were excluded. First, we examined the relationship between the presence or absence of *EGFR* mutations and clinicopathological factors, including the prognosis, such as recurrence-free survival (RFS), OS, and the cumulative incidence of recurrence (CIR).

We explained the pathological results and the administration of UFT to all patients and started administering UFT to those who wished to receive it. The UFT dose was set at 300 or 400 mg/day according to the patient's body surface area. The decision to discontinue UFT was made by the attending physician. Patients who could continue UFT were treated for up to 2 years. For the whole cohort, *EGFR*-mt and *EGFR*-wt, we examined the difference in RFS and OS between patients treated with UFT (UFT group) and those who were not treated with (no-UFT group).

Associations between clinicopathological factors were analyzed using the chi-squared test. RFS was defined as the interval from the date of surgery to the date of disease recurrence or death from any cause, censored for patients without events at the last clinic visit. OS was defined as the interval from the date of surgery until the date of death from any cause, censored for patients who were alive at the last clinic visit. Post-progression survival (PPS) was defined as the interval from the date of initial recurrence until the date of death from any cause, censored for patients who were alive at the last clinic visit. Kaplan–Meier curves were plotted for RFS, OS, and PPS, and differences between groups were analyzed using the log-rank test. The CIR was examined using Gray's competing risk analysis. For OS, the number of events was not sufficient; thus, the propensity score for each case was calculated by a logistic regression analysis using age, which was significantly associated with UFT administration (refer to the Results section), and the factors with a p-value of <0.05 in a univariate analysis (log-rank test). Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by

a multivariate analysis using the obtained propensity scores and target factors.[18] EZR ver.1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and SPSS ver.26 (SPSS Inc., Chicago, IL, USA) were used to perform the statistical analyses. Statistical significance was set at $p < 0.05$.

Results

Patients' characteristics

Table 1 shows the characteristics of the registered cases. There were 84 male and 85 female patients with an average age of 71.2 years (range: 46–88 years). Sixty-eight patients (40.2%) had tumors with ground-glass opacity (GGO) on CT images. Lobectomy was performed in 162 cases and bilobectomy was performed in seven cases. No patients underwent pneumonectomy. There were 86 *EGFR*-wt cases (50.9%) and 83 *EGFR*-mt cases (49.1%; *Exon19* deletion, n = 31; *Exon21* point mutation, n = 49 [*L858R* allele, n = 44; *L861Q* allele, n = 4; *L858R* plus *L861Q* alleles, n = 1], *Ex18* point mutation, n = 3). During the median follow-up period of 58.8 months, 37 patients developed recurrent disease, and there were 28 deaths. The 5-year RFS rate was 71.3%, and the 5-year OS rate was 86.5%.

The characteristics and prognosis of *EGFR-mt* cases

EGFR-mt cases were significantly more frequent in females ($p < 0.001$), nonsmokers ($p < 0.001$), and cases with GGO in the lesions ($p = 0.001$) than in *EGFR*-wt cases (**Table 2**). The 5-year RFS rates of *EGFR*-mt and *EGFR*-wt cases were 66.4% and 77.5%, respectively; however, the difference was not statistically significant ($p = 0.341$, **Supplementary Fig. 1A**; all supplementary files are available online.). The 5-year CIR of *EGFR*-mt and *EGFR*-wt patients were 29.5% and 15.3%, respectively. The CIR tended to be higher in *the EGFR*-mt group than in *the EGFR*-wt group ($p = 0.081$, **Supplementary Fig. 1B**). There was no significant difference in OS between the two groups ($p = 0.238$, **Supplementary Fig. 1C**). The median survival time after recurrence in the *EGFR*-mt and *EGFR*-wt groups with recurrence was 5.43 and 1.74 years, respectively, and PPS was significantly better in the *EGFR*-mt group ($p = 0.0086$, **Supplementary Fig. 1D**).

Status of postoperative UFT administration

Seventy-two of 169 cases (42.6%) underwent UFT after surgery. **Table 3** shows the relationship between

Table 1 Patients' characteristics

Sex	
Female	84 (49.7%)
Male	85 (50.3%)
Age (years)	
Average (range)	71.2 (46–88)
Smoking history	
Never	85 (50.3%)
Past or current	84 (49.7%)
GGO	
Absent	101 (59.8%)
Present	68 (40.2%)
Tumor location	
RUL	70 (41.4%)
RML	11 (6.5%)
RLL	39 (23.1%)
LUL	33 (19.5%)
LLL	16 (9.5%)
Procedure	
Lobectomy	162 (95.9%)
Bi-lobectomy	7 (4.1%)
Tumor size (mm)	
≥30	104 (61.5%)
<30	65 (38.5%)
Pleural invasion	
Absent	79 (46.7%)
Present	90 (53.3%)
Histological grade	
G1	58 (34.3%)
G2–4	111 (65.7%)
Lymphatic permeation	
Absent	126 (74.6%)
Present	43 (25.4%)
Vascular invasion	
Absent	126 (74.6%)
Present	43 (25.4%)
UFT	
UFT group	72 (42.6%)
no-UFT group	97 (57.4%)
EGFR mutation	
Absent	86 (50.9%)
Wild type	86 (50.9%)
Present	83 (49.1%)
Ex19d	31 (18.3%)
L858R	44 (26.0%)
Ex18p	3 (1.8%)
L861Q	4 (2.4%)
L858R + L861Q	1 (0.6%)

GGO: ground glass opacity; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; UFT: tegafur–uracil; *EGFR*: epidermal growth factor receptor

Table 2 Correlations between EGFR gene mutations and clinicopathological factors in LUADs

Factors	*EGFR* gene mutation		p-value
	Mutant	Wild type	
Sex			
Female	56 (67%)	28 (33%)	<0.001***
Male	27 (32%)	58 (68%)	
Age (years)			
≥75	36 (55%)	30 (45%)	0.274
<75	47 (46%)	56 (54%)	
Smoking			
Never	62 (73%)	23 (27%)	<0.001***
Past or current	21 (25%)	63 (75%)	
GGO			
Absent	39 (39%)	62 (61%)	0.001**
Present	44 (65%)	24 (35%)	
Tumor size (mm)			
≥30	53 (51%)	51 (49%)	0.635
<30	30 (46%)	35 (54%)	
Pleural invasion			
Absent	41 (52%)	38 (48%)	0.539
Present	42 (47%)	48 (53%)	
Histological grade			
G1	32 (55%)	26 (45%)	0.262
G2–4	51 (46%)	60 (54%)	
Lymphatic permeation			
Absent	60 (48%)	66 (52%)	0.597
Present	23 (53%)	20 (47%)	
Vascular invasion			
Absent	64 (51%)	62 (49%)	0.484
Present	19 (44%)	24 (56%)	
UFT			
UFT group	38 (53%)	34 (47%)	0.440
No-UFT group	45 (46%)	52 (54%)	

**p <0.01, ***p <0.001.

LUADs: lung adenocarcinomas; *EGFR*: epidermal growth factor receptor; GGO: ground glass opacity; UFT: tegafur–uracil

Table 3 Correlations between UFT administration and clinicopathological factors in LUADs

Factors	UFT group	no-UFT group	p-value
Sex			
Female	39 (46%)	45 (54%)	p = 0.353
Male	33 (39%)	52 (61%)	
Age (years)			
≥75	15 (23%)	51 (77%)	p <0.001***
<75	57 (55%)	46 (45%)	
Smoking			
Never	42 (49%)	43 (51%)	p = 0.087
Past or current	30 (55%)	54 (45%)	
GGO			
Absent	39 (39%)	62 (61%)	p = 0.209
Present	33 (45%)	35 (55%)	
Tumor size (mm)			
≥30	46 (44%)	58 (56%)	p = 0.633
<30	26 (40%)	39 (60%)	
Pleural invasion			
Absent	39 (49%)	40 (51%)	p = 0.119
Present	33 (37%)	57 (63%)	
Histological grade			
G1	25 (43%)	33 (57%)	p = 1.000
G2–4	47 (42%)	64 (58%)	
Lymphatic permeation			
Absent	52 (41%)	74 (59%)	p = 0.594
Present	20 (47%)	23 (53%)	
Vascular invasion			
Absent	52 (41%)	74 (59%)	p = 0.594
Present	20 (47%)	23 (53%)	
EGFR mutation			
Wild type	34 (40%)	52 (60%)	p = 0.440
Mutant	38 (46%)	45 (54%)	

***p <0.001.

UFT: tegafur–uracil; LUADs: lung adenocarcinomas; GGO: ground glass opacity; *EGFR*: epidermal growth factor receptor

UFT administration and clinicopathological factors. When limited to patients under 75 years of age, 57 of 103 (55.3%) patients underwent UFT. On the other hand, 15 of 66 (22.7%) patients ≥75 years of age underwent UFT; the difference was statistically significant (p <0.001). No other factors were associated with UFT administration. The reasons for not taking UFT were old age (n = 51), preoperative comorbidities (n = 10), cases in which GGO accounted for a large proportion of the lesion (n = 7), poor postoperative condition (n = 16), and patient refusal (n = 13). UFT was discontinued less than 1 year after surgery in 23 of 72 patients (31.9%), among whom 16 of 23 patients (69.6%) discontinued administration within 3 months. The reasons for discontinuation were upper gastrointestinal symptoms in 12 of 23 patients (52.2%), liver dysfunction (n = 5), fatigue (n = 1), allergic symptoms (n = 2), pulmonary fistula (n = 2), and gynecomastia (n = 1).

Prognostic impact of UFT administration

In the whole cohort, the 5-year RFS rates of the UFT group and the no-UFT group were 76.9% and 67.3%, respectively, but did not differ to a statistically significant extent (p = 0.139, **Fig. 1A**). A univariate analysis showed that OS was significantly better in the UFT group than in the no-UFT group (p = 0.023, **Fig. 1B**).

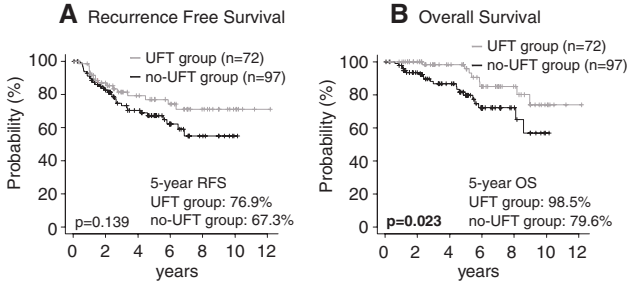

Fig. 1 Correlation between UFT administration and the prognosis according to the presence of *EGFR* mutation. These figures show the differences in the prognosis between patients with or without UFT administration in the entire cohort (RFS: **A**, OS: **B**). Survival curves for the UFT and no-UFT groups are represented by gray and black lines, respectively. UFT: tegafur–uracil; *EGFR*: epidermal growth factor receptor; RFS: recurrence-free survival; OS: overall survival

Table 4 A univariate analysis and multivariate logistic regression analysis of the factors associated with OS in LUADs

Factors	Univariate p-value	Multivariate		
		HR	95% CI	p-value
Sex	0.011*	0.539	0.226–1.284	0.163
Age	0.081	1.466	0.683–3.145	0.326
Smoking	0.036*	1.126	0.463–2.740	0.794
GGO	0.006**	0.415	0.148–1.162	0.094
Tumor size	0.049*	0.696	0.325–1.493	0.352
Pleural invasion	0.074	1.010	0.422–2.419	0.982
Histological grade	0.216	1.127	0.495–2.566	0.775
Lymphatic permeation	0.452	1.021	0.464–2.243	0.959
Vascular invasion	0.298	1.223	0.548–2.730	0.624
EGFR mutation	0.238	0.902	0.418–1.945	0.792
UFT	0.023*	0.504	0.217–1.172	0.112

*p <0.05, **p <0.01.
OS: overall survival; LUADs: lung adenocarcinomas; HR: hazard ratio; CI: confidence interval; GGO: ground glass opacity; *EGFR*: epidermal growth factor receptor; UFT: tegafur–uracil

However, the administration of UFT was not an independent prognostic factor for OS in a multivariate logistic regression analysis that included age, sex, smoking history, presence of GGO, and tumor size as covariates (**Table 4**; p = 0.112, HR: 0.504, 95% CI: 0.217–1.172). In *EGFR*-wt cases, the RFS (p = 0.022, **Fig. 2A**) and OS (p = 0.023, **Fig. 2B**) of the UFT group were significantly better than those of the no-UFT group. Moreover,

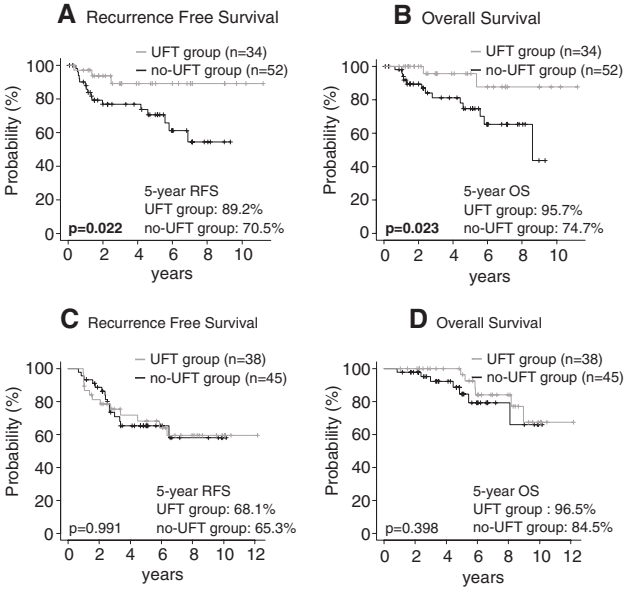

Fig. 2 Correlation between UFT administration and the prognosis according to the presence of *EGFR* mutation. These figures show the differences in the prognosis between patients with *EGFR*-wt cases (RFS: **A**, OS: **B**) and *EGFR*-mt cases (RFS: **C**, OS: **D**). Survival curves for the UFT and no-UFT groups are represented by gray and black lines, respectively. UFT: tegafur–uracil; *EGFR*: epidermal growth factor receptor; *EGFR*-wt: *EGFR* wild-type; *EGFR*-mt: *EGFR* mutant; RFS: recurrence-free survival; OS: overall survival

the administration of UFT was an independent favorable prognostic factor for OS in a multivariate logistic regression analysis that included age as a covariate (**Table 5**; p = 0.031, HR: 0.185, 95% CI: 0.040–0.858). In *EGFR*-mt cases, there was no difference in RFS (p = 0.991, **Fig. 2C**) or OS (p = 0.398, **Fig. 2D**) between the UFT and no-UFT groups. The administration of UFT was not identified as an independent prognostic factor for OS in a multivariate logistic regression analysis that included sex, age, presence of GGO, tumor size, and pleural invasion as covariates (**Table 6**; p = 0.266, HR: 0.521, 95% CI: 0.157–1.667).

Discussion

There are several reports on differences in the efficacy of cytotoxic anticancer agents, including UFT, depending on the presence or absence of *EGFR* mutations at various pathological stages.[15–17] As there is a lack of clinical data on adjuvant chemotherapy in patients with early stage NSCLC, this is the first real-world report focusing on stage IB NSCLC according to the TNM seventh

Table 5 A univariate analysis and multivariate logistic regression analysis of the factors associated with OS in *EGFR*-wt

Factors	Univariate p-value	Multivariate		
		HR	95% CI	p-value
Sex	0.240	0.507	0.143–1.801	0.294
Age	0.767	1.372	0.472–3.984	0.561
Smoking	0.467	1.337	0.373–4.808	0.656
GGO	0.223	0.441	0.099–1.960	0.282
Tumor size	0.608	0.834	0.300–2.319	0.728
Pleural invasion	0.642	1.184	0.421–3.332	0.749
Histological grade	0.477	1.485	0.470–4.689	0.501
Lymphatic permeation	0.793	1.318	0.405–4.292	0.647
Vascular invasion	0.932	1.073	0.341–3.378	0.905
UFT	0.023*	0.185	0.040–0.858	0.031*

*p <0.05.

OS: overall survival; *EGFR*: epidermal growth factor receptor; *EGFR*-wt: *EGFR* wild-type; HR: hazard ratio; CI: confidence interval; GGO: ground glass opacity; UFT: tegafur–uracil

Table 6 A univariate analysis and multivariate logistic regression analysis of the factors associated with OS in *EGFR*-mt

Factors	Univariate p-value	Multivariate		
		HR	95% CI	p-value
Sex	0.038*	0.376	0.122–1.154	0.087
Age	0.016*	3.807	1.160–12.494	0.027*
Smoking	0.058	1.969	0.633–6.135	0.242
GGO	0.019*	0.421	0.108–1.643	0.213
Tumor size	0.019*	0.586	0.176–1.951	0.384
Pleural invasion	0.040*	1.223	0.315–4.753	0.771
Histological grade	0.304	1.356	0.432–4.259	0.602
Lymphatic permeation	0.147	1.347	0.427–4.254	0.611
Vascular invasion	0.107	2.004	0.644–6.232	0.230
UFT	0.398	0.521	0.157–1.667	0.266

*p <0.05.

OS: overall survival; *EGFR*: epidermal growth factor receptor; *EGFR*-mt: *EGFR* mutant; HR: hazard ratio; CI: confidence interval; GGO: ground glass opacity; UFT: tegafur–uracil

edition (tumor >3 cm but ≤5 cm or tumor ≤3 cm with visceral pleural invasion and no lymph node and distant metastases).[11] The major finding of our study was that postoperative UFT treatment improved the prognosis in *EGFR*-wt cases, whereas it was not observed to affect the prognosis of *EGFR*-mt cases.

In the whole cohort, although a univariate analysis showed that the OS of the UFT group was significantly better than that of the no-UFT group, the administration of UFT was not an independent prognostic factor in the multivariate logistic regression analysis. In the JLCRG trial, T2 was defined by a tumor diameter of >3 cm with no upper limit.[8] This point is different from the present study, which targeted stage IB with a tumor diameter of >3 cm to ≤5 cm and/or the presence of pleural invasion.[11] A recent multicenter real-world data study of patients with resected stage I LUAD with a tumor diameter of >2 cm to ≤5 cm in Japan reported that the administration of UFT did not significantly improve OS.[19] This result supports the results observed in the entire cohort of our study. However, this study did not examine the effects of UFT with or without *EGFR* mutations.

In *EGFR*-wt cases, the RFS of the UFT group was significantly better than that of the no-UFT group. Regarding OS, the administration of UFT was independently associated with favorable OS in a multivariate logistic regression analysis. In the Japan Intergroup Trial of Pemetrexed Adjuvant Chemotherapy for completely resected Non-squamous Non-small cell lung cancer (JIPANG) trial, which compared cisplatin plus vinorelbine and cisplatin plus pemetrexed as adjuvant therapy for completely resected stage II–III nonsquamous NSCLC, the effect of cytotoxic anticancer agents against *EGFR*-mt cases was lower than that against *EGFR*-wt cases.[15,20] Regarding the effect of UFT on stage I-IIIA LUAD, UFT significantly improved OS in *EGFR*-wt cases compared to that in *EGFR*-mt cases.[16] Conversely, there was no difference in OS between *EGFR*-mt and *EGFR*-wt cases. The PPS of *EGFR*-mt cases was significantly better than that of *EGFR*-wt cases, indicating the excellent life-prolonging effect of EGFR-TKIs in *EGFR*-mt cases after recurrence, as previously reported.[21] In *EGFR*-mt patients, the RFS and OS did not differ according to the presence or absence of UFT administration. The influence of *EGFR* mutation status on the efficacy of UFTs has been studied previously. *EGFR* signaling has been reported to decrease the activity of dihydropyrimidine dehydrogenase, which is involved in the catabolism of fluorouracil.[22] In an in vitro study, the 50% inhibitory concentration of UFTs in *EGFR*-mut cells was higher in adenocarcinoma cell lines than in wild-type cells.[16] In addition, antiapoptotic activity via the Akt and signal transducer and activator of transcription (STAT) pathways[23] is highly activated in

EGFR-mutant tumors, which may reduce the apoptotic effect of UFT.[24] These may be related to the different effects of UFTs in NSCLC patients with and without *EGFR* mutations. Furthermore, a recent study suggested the concept of high-risk stage I LUAD, defined as an invasive component size of >2 cm, visceral pleural invasion, or vascular invasion.[25] Adjuvant chemotherapy, including UFT for high-risk stage I LUAD, did not improve the 5-year RFS in *EGFR*-mt cases,[17] which is consistent with the present study and may be related to the high recurrence rate of stage IB LUADs with *EGFR* mutations.

EGFR gene mutations may predict the effect of cytotoxic anticancer drugs; therefore, it is important to search for gene mutations in resected stage IB LUAD specimens. The ADAURA trial demonstrated the usefulness of postoperative adjuvant therapy with osimertinib for *EGFR*-mt cases, even in stage IB.[14] Since postoperative adjuvant therapy with UFT in stage IB *EGFR*-mt cases is less effective, it is also desirable to examine the effect of postoperative adjuvant therapy with osimertinib Japanese patients.

In this study, according to the TNM seventh edition, there was no association between tumor size and prognosis. According to the current guidelines of the Japan Lung Cancer Society, the tumor size rather than the invasion size was adopted as the criterion for postoperative adjuvant therapy with UFT.[26] The TNM eighth edition introduced the concept of invasion size as a T descriptor for the first time, based on the tumor size of the invasive solid portion of the part-solid nodule and the total size of the solid nodule.[27] Current clinical trials were based on the TNM seventh or earlier edition, so it is difficult to simply convert the results in the TNM eighth edition. However, the evaluation of the relationship between tumor size and invasion size and the proportion of visceral pleural invasion for the target population of this study is of great importance (**Supplementary Table 1**). This study did not include adenocarcinoma in situ and had only five cases of minimally invasive adenocarcinoma. There were many cases of visceral pleural invasion among those with small invasion size. To the best of our knowledge, there are no data on the efficacy of UFT based on pathological stage in TNM eighth edition. We conducted an exploratory analysis for the contribution of the invasion size, and invasion size also did not have a significant relationship with OS ($p = 0.976$, HR: 1.001). These data suggest that there is no difference in prognosis based on size in the stage IB LUAD, even in the TNM eighth edition. Patients with early-stage LUAD with a small invasion size had an apparent low risk of recurrence and may not require administration of UFT, although it is difficult to define the specific size for not administering UFT in this study.

The present study was associated with some limitations. It included a small number of patients who were managed at a single institute. The prevalence of *EGFR*-mt cases may be high in East Asia, including Japan, and about half of the cases in this study were classified into the *EGFR*-mt group. However, because this study was conducted in a limited area, it cannot be denied that the results represent findings specific to that area. In addition, since this is a retrospective study and the administration and continuation of UFT were based on the judgment of the attending physician, there may be invisible biases. Randomized controlled trials involving a large number of patients in the latest version of the TNM classification and a wider geographic area of Japan would be desirable to investigate the effects of UFT on stage IB *EGFR*-mt cases in more detail.

Conclusion

The present study confirmed that adjuvant therapy with UFT for stage IB LUAD is useful for *EGFR*-wt cases, suggesting that UFT is less effective for *EGFR*-mt cases. For *EGFR*-positive stage IB LUAD, the result of the ADAURA trial was favorable, but the standard adjuvant therapy for stage IB LUAD in Japan is UFT. Thus, clinical trials of adjuvant targeted therapy for *EGFR* mutation-positive stage IB LUAD should also be conducted in Japan.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Epidemiological and Related Studies, Sakuragaoka Campus, Kagoshima University (approval number: 230003epi), and conformed to the principles outlined in the Declaration of Helsinki. Research participants and their relatives could opt out by viewing the research content hosted online.

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Data availability statement

All data are included in this article. Further inquiries can be directed to the corresponding author.

Authors' contributions

MA, RM, and KU gave the initial idea. MA, GK, AHT, TS, and KM treated the patient. MA, RM, GK, AHT, and KU recollected the data. MA and RM drafted the manuscript. All authors read and approved the final manuscript.

Disclosure statement

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

Supplementary Information (available online)

Supplementary Fig. 1 Correlation between *EGFR* mutation and the prognosis These figures show the differences in RFS (**A**), CIR (**B**), and OS (**C**) between patients with and without *EGFR* mutations in stage IB LUAD. **Supplementary Fig. 1**(**D**) shows the difference in PPS depending on the presence or absence of *EGFR* mutations in the recurrent cases. Survival curves for *EGFR*-mt and *EGFR*-wt are represented by gray and black lines, respectively. *EGFR*: epidermal growth factor receptor; RFS: recurrence-free survival; CIR: cumulative incidence of recurrence; OS: overall survival; LUAD: lung adenocarcinoma; PPS: post-progression survival; *EGFR*-wt: *EGFR* wild-type; *EGFR*-mt: *EGFR* mutant

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