Original Article

Efficacy of platinum-based adjuvant chemotherapy for epidermal growth factor receptor-mutant lung adenocarcinoma

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Background: The ADAURA trial reported that osimertinib improved overall survival (OS) as an adjuvant chemotherapy for pathological stage IB–IIIA epidermal growth factor receptor (EGFR) mutant lung cancer compared with a placebo. Currently, platinum-based adjuvant chemotherapy is the standard treatment for patients with or without EGFR mutations. This study aimed to evaluate the efficacy of platinum-based adjuvant chemotherapy in patient with stage II–IIIA EGFR mutant lung adenocarcinoma.

Methods: We collected the medical records of consecutive patients who underwent surgical resection for lung adenocarcinoma between 2005 and 2012 at the four participating institutions. The data of 173 patients with different EGFR mutation status were retrospectively evaluated to determine the efficacy of platinum-based adjuvant chemotherapy for OS and recurrence-free survival (RFS). We further analyzed OS using the inverse probability of treatment weighting method with propensity scores.

Results: The median age was 69 years (range, 45–85 years); 95 (54.9%) were male and 74 (42.8%) had EGFR mutations. A total of 43 patients with EGFR mutants (58.1%) and 43 patients with wild-type EGFR tumors (43.4%) received platinum-based adjuvant chemotherapy. No differences in RFS and OS were observed between EGFR mutant and wild-type EGFR in lung adenocarcinoma without adjuvant therapy. However, wild-type EGFR showed an improvement in OS with platinum-based adjuvant chemotherapy in inverse probability of treatment weighting analysis, whereas those with EGFR mutations showed no significant difference in OS between the surgery-only group and the adjuvant group. The deletion of exon 19 and exon 21 L858R point mutation showed no significant differences in OS between the surgery-only group and the adjuvant group, respectively. The hazard ratio (HR) exceeded 1 for uncommon EGFR mutations.

Conclusions: Platinum-based adjuvant chemotherapy may be less effective for EGFR-mutant lung adenocarcinoma, regardless of the mutation type.

Keywords: Lung cancer; epidermal growth factor receptor mutation (EGFR mutation); adjuvant chemotherapy; platinum-based chemotherapy

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Introduction

Background

Lung cancer is one of the leading causes of death worldwide, and perioperative treatment with a focus on surgery is a major component of curative treatment. A method called "radical lobectomy", which involves the removal of one lobe of the lung, hilar and mediastinal lymph nodes, reported by Cahan in 1960, has become the standard surgical technique for lung cancer (1). However, the 5-year overall survival (OS) rates of patients with pathological stages IB (73%), IIA (65%), IIB (56%), and IIIA (41%), which are indications for surgery, were not satisfactory (2). The primary issue in improving treatment outcomes is the control of distant metastasis; however, the development and improvement of perioperative systemic treatments are also important. In 2005, Hamada *et al.* reported a meta-analysis of postoperative tegafur-uracil therapy (3). A meta-analysis of postoperative cisplatin combination therapy by Pignon *et al.* in 2008 showed a 5% improvement in the 5-year survival of patients with stage I–III non-small cell lung cancer (NSCLC) (4). In addition, a subgroup analysis of cisplatin plus vinorelbine showed 11% and 15% improvement in survival for stage II and stage III NSCLC, respectively (5). Based on this evidence, postoperative adjuvant chemotherapy has been used to treat NSCLC for over 10 years.

Rationale and knowledge gap

In 2020, Wu *et al.* reported the efficacy of postoperative osimertinib therapy for epidermal growth factor receptor (EGFR) mutant lung cancer (6); findings from the study showed a significant improvement in disease-free survival (DFS) in patients with pathological stage II–IIIA lung adenocarcinoma, with 44% and 90% [hazard ratio (HR), 0.17] 2-year DFS in the control and osimertinib groups, respectively. In 2023, Tsuboi *et al.* reported an improvement in OS with osimertinib adjuvant therapy (7), which may replace the standard treatment for EGFR-mutant adenocarcinoma. On the other hand, developments have been made in perioperative treatment using immune checkpoint inhibitors. The IMpower010 study was a phase III trial that compared atezolizumab with or without platinum-based combination therapy in patients with completely resected stage IB (tumor size ≥4 cm) to stage IIIA NSCLC according to the 7th edition of the Union for International Cancer Control (8). In the study, the atezolizumab group showed significantly prolonged DFS (HR, 0.66) in the population with programmed death ligand 1 ≥1% in stage II–IIIA. Only patients with EGFR mutations in the same population also showed a favorable result (HR, 0.57). Therefore, developing an optimal strategy for adjuvant therapy for patients with EGFR mutations is crucial; however, there is debate over the relationship between EGFR mutation status and chemotherapy efficacy and prognosis in patients with advanced NSCLC (9). Platinum doublet postoperative chemotherapy was reportedly less effective in EGFR mutation-positive NSCLC (10).

Objective

This study aimed to investigate the efficacy of platinum-based adjuvant chemotherapy in patients with different types of EGFR mutation. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1323/rc).

Highlight box

Key findings

- Platinum-based adjuvant chemotherapy has a poor survival benefit for patients with epidermal growth factor receptor-mutant lung adenocarcinoma.

What is known and what is new?

- The effect of adjuvant chemotherapy was similar for deletion 19 and L858R.
- There was no difference in prognosis between EGFR mutants and wild types without adjuvant therapy.

What is the implication, and what should change now?

- Molecular-targeted therapy should be administered immediately after surgery.

Methods

Patients

This study was an additional analysis of our previous study (11,12). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review boards of Tohoku University and the Japanese Northern East Area Thoracic Surgery Study Group (ID: 2016-1-311), and individual

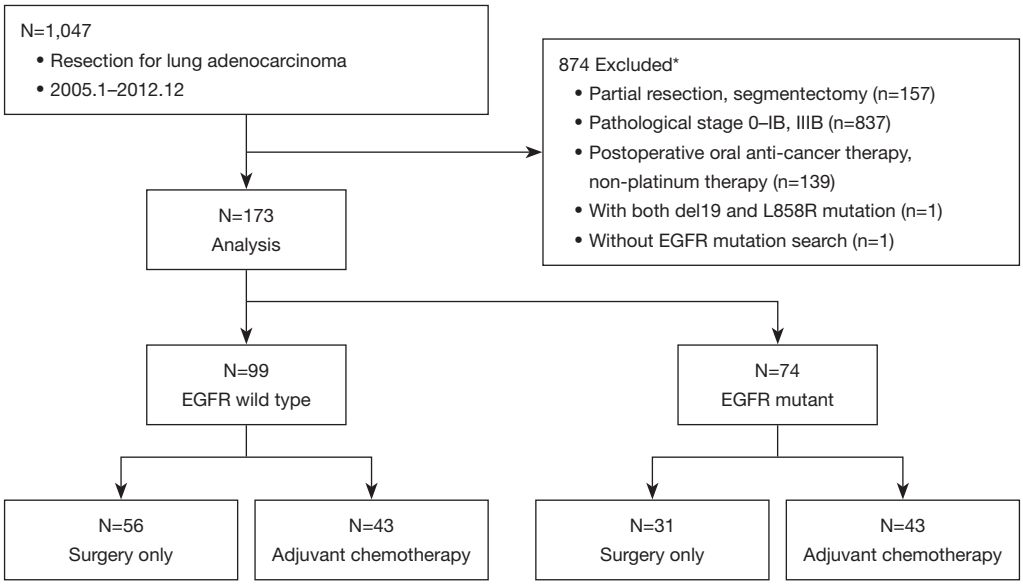

Figure 1 Flow diagram. *, there are duplicate cases in these cases. EGFR, epidermal growth factor receptor.

consent for this retrospective analysis was waived. The data of patients with different EGFR mutation status were retrospectively evaluated to determine the efficacy of platinum-based adjuvant chemotherapy for OS and recurrence-free survival (RFS). We further analyzed OS using the inverse probability of treatment weighting method with propensity scores.

We collected data on consecutive patients who underwent complete resection of lung adenocarcinoma between January 2005 and December 2012 at Tohoku University Hospital, Fukushima Medical University Hospital, Yamagata Prefectural Central Hospital, and Miyagi Cancer Center. The tumor of all the patients were examined for EGFR mutations. The medical records of 1,047 enrolled patients were collected. Patients with pIIA–IIIA lung adenocarcinoma who underwent lung lobectomy were included, whereas those who received preoperative treatment or postoperative oral anti-cancer treatment were excluded. A total of 173 patients were included in this study (*Figure 1*). Platinum-based adjuvant chemotherapy was administered at the discretion of the oncologist. Patients were evaluated at 3 to 6 months intervals for the first 5 years; thereafter, the interval was extended to once per year. The follow-up evaluation included a physical examination, chest radiography, blood examination (including tumor markers), and chest computed tomography (CT). Further evaluations, including brain magnetic resonance imaging and positron emission tomography/CT were performed whenever any symptoms or signs of recurrence were detected. All patients were followed-up for at least 5 years after surgery. The diagnosis of recurrence was based on compatible physical examination and diagnostic imaging features; histological confirmation of recurrence was not mandatory.

Clinicopathologic evaluations

All patient information was extracted from the electronic medical records and databases at each institution. The clinical and pathological staging was reassessed according to the eighth edition of the tumor-node-metastasis (TNM) classification (13), and histological typing was performed according to the World Health Organization classification (14). Each institution adopted an individual commercial method to identify EGFR mutations in the tumors, such as the PCR-invader method (BML, Tokyo, Japan), direct sequencing method (SRL, Tokyo, Japan), or PNA-LNA PCR Clamp method (LSI Medience Corporation, Tokyo, Japan), following the manufacturer's protocols. In this study, we defined the deletion of exon 19 and exon 21 L858R point mutation as common EGFR mutations, and exon 18 G719A, exon 18 G719S, *de novo* exon 20 T790M, and exon 21 L861Q as uncommon mutations.

Statistical analysis

OS was defined as the period from surgery to death

from any cause or censored at the final follow-up. RFS was defined as the period from surgery to relapse, death from any cause, or censored at final follow-up. Patient characteristics were summarized using frequencies and descriptive statistics, such as medians and ranges. Cases with loss to follow-up were treated as censored. We used the chi-square test and Wilcoxon rank-sum tests to compare the between EGFR wild-type and mutant groups. OS and RFS were estimated using the Kaplan-Meier method.

To examine risk factors for OS in the overall population, HRs and its confidence intervals (CIs) were estimated by multivariate proportional hazards model, including prognostic factors such as age, sex (male/female), smoking history (ever/never), serum carcinoembryonic antigen (CEA) level, pathological stage (III/II), platinum-based adjuvant therapy (yes/no), intrathoracic recurrence (yes/no), extrathoracic recurrence (yes/no), post-recurrence tyrosine kinase inhibitor (TKI) (yes/no) and EGFR mutation (yes/no) as explanatory variables.

To investigate the efficacy of platinum-based adjuvant therapy, propensity scores were calculated using age, sex, smoking history, and pathological T and N factors. Cox proportional hazards regression analysis was performed using the inverse probability of treatment-weighting (IPTW) method with the propensity scores. Since there was little missing data, complete-case analysis was performed.

IPTW analysis was performed using the R Release version 4.3 statistical software suite (The R Foundation for Statistical Computing, Vienna, Austria). Other statistical analyses were performed using the JMP Release version 17.1 statistical software suite (JMP Institute, Cary, NC, USA). Statistical significance was set at $P<0.05$ without adjusting for multiple tests. Confidence level was set to 0.95.

Results

Patient characteristics

The clinicopathological characteristics of the study patients are presented in *Table 1*. There were 10 missing data in vascular and lymphatic invasion, respectively. There were 95 males and 78 females, with ages ranging from 45–85 years, and a median age of 69 years. The median smoking index was 165 (range, 0–4,000). The median serum CEA was 4 ng/mL (range, 0–889 ng/mL). Overall, 63, 34, and 76 patients had pathological stages IIA, IIB, and IIIA, respectively, and 74 patients harbored EGFR mutations. Platinum-based adjuvant therapy was administered to 86 patients.

Survival analysis

The median follow-up was 5.0 and 8.0 years for all patients and censored patients, respectively. One hundred and twenty recurrences and 110 deaths were observed in this study. In the overall population, both RFS and OS were better in pathological stage II compared to stage III (5-year RFS, 39.0% *vs.* 13.5%; HR, 0.58; 95% CI: 0.41–0.82; 5-year OS, 62.9% *vs.* 41.7%; HR, 0.70; 95% CI: 0.48–1.02) (Figure S1). In lung adenocarcinoma without adjuvant therapy, no differences in RFS and OS were observed between EGFR mutant and wild-types (5-year RFS, 25.8% *vs.* 32.1%; HR, 0.98; 95% CI: 0.58–1.65; 5-year OS, 38.7% *vs.* 48.2%; HR, 1.00; 95% CI: 0.57–1.74) (*Figure 2*). In EGFR wild-type tumors, the OS of the adjuvant group tended to be better than that of the surgery-only group, although the difference was not significant (HR, 0.66; 95% CI: 0.40–1.10). In contrast, in EGFR mutant tumors, no difference was observed between the adjuvant and surgery-only groups (HR, 0.81; 95% CI: 0.45–1.45). Analysis by EGFR mutation type showed no significant differences were found for the deletion of exon 19, exon 21 L858R point mutation, and uncommon mutations (*Table 2*, *Figure 3A*). In multivariate analysis of OS, age (HR 1.03, 95% CI: 1.00–1.06), sex (HR 2.04, 95% CI: 1.13–3.70), platinum-based adjuvant therapy (HR 0.49, 95% CI: 0.30–0.81) and extrathoracic recurrence (HR 2.18, 95% CI: 1.16–4.09) remained as independent prognostic factors. Pathological stage (HR 1.15, 95% CI: 0.73–1.81), post-recurrence TKI (HR 2.10, 95% CI: 0.98–4.05) and EGFR mutation (HR 0.67, 95% CI: 0.32–1.43) did not remain as independent prognostic factors (Figure S2).

Inverse probability of treatment weighting analysis

Cox proportional hazard regression analysis was performed using the IPTW method to eliminate bias, with age, sex, pathological T factor, and pathologic N factor as propensity scores. No extreme propensity scores were observed (Table S1). The IPTW method showed that the OS of the adjuvant group was significantly better than that of the surgery-only group in EGFR wild-type tumors (HR, 0.50; 95% CI: 0.26–0.97). In contrast, for EGFR mutant tumors, no difference was observed between the adjuvant and surgery-only groups (HR, 0.57; 95% CI: 0.31–1.08). Analysis of each EGFR mutation type showed that the

Table 1 Patient characteristics with or without EGFR mutation

Characteristic	Subtypes	EGFR wild type (n=99)	EGFR mutant (n=74)	P value
Age (years), median [range]		70 [45–85]	67.5 [51–82]	0.47
Sex	Male	68	27	<0.01
	Female	31	47	
Smoking history	Ever smoker	68	25	<0.01
Smoking index, median [range]		600 [0–2,000]	0 [0–4,000]	<0.01
Serum CEA, ng/mL, median [range]		3.6 [0–889]	4.1 [0.5–283]	0.79
Pathological stage	II	57	40	0.64
	III	42	34	
Platinum-based adjuvant therapy	No	56	31	0.06
	Yes	43	43	
Pleural invasion	None	53	41	0.81
	Present	46	33	
Vascular invasion	None	62	37	0.10
	Present	30	34	
Lymphatic invasion	None	48	28	0.19
	Present	44	43	
Recurrence	Total	66	54	0.37
	Intrathoracic	45	35	
	Extrathoracic	30	26	
	Unknown	1	0	
Post-recurrence TKI	Administered	9	44	<0.01
EGFR mutation	Exon 21 L858R	NA	31	
	Exon 19 del	NA	31	
	Uncommon	NA	12	

EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigen; TKI, tyrosine kinase inhibitor; NA, not available.

deletion of exon 19 and the L858R point mutation in exon 21 showed no significant differences in OS (HR, 0.71; 95% CI: 0.29–1.76 *vs*. HR, 0.69; 95% CI: 0.28–1.69). The HR exceeded 1 for uncommon EGFR mutations (HR, 1.16; 95% CI: 0.27–4.92) (*Table 2*, *Figure 3B*).

Discussion

Key findings

In this study, we evaluated the prognosis of EGFR-mutant and wild-type lung adenocarcinomas with and without chemotherapy. Our results showed no significant difference in OS between the surgery-only group and adjuvant chemotherapy groups, regardless of the presence or absence of EGFR mutations before IPTW analysis. The results of the IPTW analysis showed that chemotherapy was effective for lung adenocarcinoma with wild-type EGFR in terms of OS but not significantly for EGFR-mutant. Therefore, our results suggest that the effect of adjutant of platinum-based adjuvant chemotherapy on the OS is relatively lower in the EGFR-mutant lung adenocarcinoma than to the wild-type EGFR. In the EGFR mutation group in this study, almost all patients with recurrence received EGFR-TKI. This result is probably because EGFR-TKI has a significant

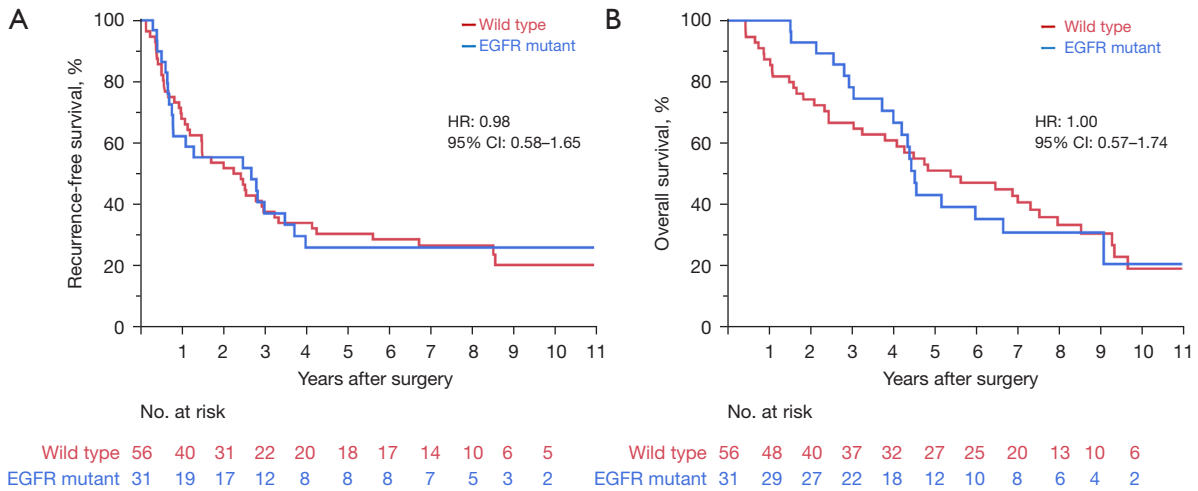

Figure 2 Recurrence-free survival (A) and overall survival (B) curves with or without EGFR mutation. EGFR, epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval.

Table 2 Univariate analysis

EGFR mutation	Entire cohort		IPTW	
	HR	95% CI	HR	95% CI
All cases	0.74	0.51–1.08	0.66	0.44–1.01
Wild type	0.66	0.40–1.10	0.50	0.26–0.97
EGFR mutant	0.81	0.45–1.45	0.57	0.31–1.08
Del19	0.63	0.27–1.51	0.71	0.29–1.76
L858R	0.76	0.29–1.98	0.69	0.28–1.69
Uncommon	1.16	0.25–5.31	1.16	0.27–4.92

EGFR, epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment-weighting.

impact on OS after EGFR-mutant recurrence with or without the use of platinum-based adjuvant chemotherapy.

Furthermore, we examined the effects of adjuvant therapy on each type of EGFR mutation. The deletion of exon 19 and the L858R point mutation in exon 21 showed no significant difference in OS between the surgery-only and adjuvant chemotherapy groups, respectively. The effects of adjuvant chemotherapy were similar for the deletion of exon 19 and the L858R point mutation in exon 21. In uncommon EGFR mutations, the HR exceeded 1, although this was a reference value owing to the small number of cases. It may be main cause that they had poor sensitivity to both postoperative platinum-based chemotherapy and EGFR-TKI used after recurrence.

Strengths and limitations

This study had some limitations. First, IPTW analysis was performed to eliminate selection bias. However, this was a retrospective study, and selection bias could not be eliminated. Because the compliance rate of adjuvant chemotherapy in clinical practice is about half, randomized controlled trials may be necessary to accurately evaluate it. Furthermore, the type of platinum-based chemotherapy and the number of treatment cycles were based on four courses of vinorelbine, but left to the discretion of the attending physician. Therefore, bias may not have been eliminated. Second, the number of patients was small; hence obtaining a sufficient number of eligible patients at a single institution was difficult because stage II–III EGFR mutant lung adenocarcinoma was the target. Therefore, we collected cases from multiple centers. The results of this study need to be validated on a larger scale in future research.

Comparison with similar research

There are several reports on the effects of platinum-based chemotherapy based on the EGFR status in advanced lung cancer, which may be helpful in predicting the efficacy of platinum-based adjuvant chemotherapy in patients with EGFR-mutant lung cancer (15-28). There are both reports of advanced NSCLC with EGFR mutations responding poorly and favorably to platinum-based chemotherapy compared to wild-type NSCLC. However, neither report compared the effect of chemotherapy with or without

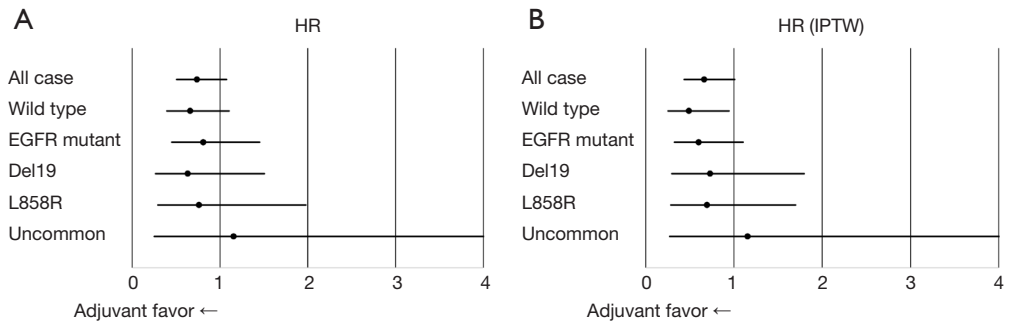

Figure 3 Forest plots about the effect of adjuvant chemotherapy for OS at each EGFR status. Before (A) and after (B) IPTW analysis. HR, hazard ratio; EGFR, epidermal growth factor receptor; IPTW, inverse probability of treatment-weighting; OS, overall survival.

treatment, but rather compared chemotherapy-treated EGFR-mutant patients with wild-type patients. The fact that the difference in biological grade between the EGFR-mutant and wild-type is not taken into account is probably the reason for this inconsistent result. Therefore, the efficacy of platinum-based chemotherapies remains unclear.

On the other hand, there are few reports on the effects of postoperative adjuvant chemotherapy based on the EGFR status. Suehisa *et al.* reported that EGFR mutant cells were less sensitive to fluorouracil than the wild type *in vitro*, and EGFR-mutant lung adenocarcinoma showed no survival benefit from tegafur-uracil adjuvant therapy (29). Takahashi *et al.* reported that EGFR mutations were predictors of poor response to platinum-based adjuvant chemotherapy in patients with stage II–IIIA NSCLC (10). However, their study could not compare with and without adjuvant chemotherapy. In this study, we investigated the efficacy of platinum-based adjuvant chemotherapy in EGFR-mutant lung cancer by comparing with and without chemotherapy.

Explanations of findings

It remains debatable whether EGFR mutations are prognostic factors of NSCLC. In 2021, Suda *et al.* reported an association between EGFR status and prognosis (30) and that EGFR mutations were a prognostic factor for RFS and OS. Izar *et al.* also reported that the RFS in EGFR-mutant NSCLC was better than that in the wild-type (31). In contrast, we previously reported that EGFR status was not associated with prognosis (11), which is consistent with similar reports (32-35). However, in all reports, most patients had pathological stage I disease. In this study targeted at pathological stage II–III lung adenocarcinoma, EGFR status was not a prognostic factor for RFS and OS in lung adenocarcinoma without adjuvant therapy. In contrast, EGFR mutation had a better prognosis for OS in the short term but is similar to the wild-type in the long term. This may be due to the effects of EGFR-TKI administration after relapse.

Implications and actions needed

This study suggested that platinum-based adjuvant therapy was unlikely to improve survival in EGFR-mutant lung adenocarcinoma, and that there was no difference in prognosis between EGFR mutants and wild types without adjuvant therapy. Therefore, selecting effective adjuvant strategies for EGFR mutations is necessary to further improve its prognosis. The ADAURA trial showed that osimertinib adjuvant therapy improved DFS and OS in EGFR mutant NSCLC (7). Platinum-based adjuvant chemotherapy in the ADAURA trial was left to the discretion of the attending oncologist, and the necessity of adjuvant chemotherapy remains controversial. If platinum-based adjuvant chemotherapy is less effective in patients with EGFR mutations, as shown by the results of this study, then molecular-targeted therapy should be administered immediately after surgery.

Conclusions

This study suggests that the effect of adjutant platinum-based chemotherapy on the OS is relatively lower with EGFR-mutant lung adenocarcinoma. In addition, there may be no difference in the prognosis between EGFR mutants and wild-type without adjuvant therapy. Therefore, it is necessary to consider optimal perioperative treatment strategies, including molecular targeted therapy and

immune checkpoint inhibitors, because platinum-based adjuvant therapy is less effective in EGFR mutant lung adenocarcinoma.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1323/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1323/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1323/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review boards of Tohoku University and the Japanese Northern East Area Thoracic Surgery Study Group (ID: 2016-1-311), and individual consent for this retrospective analysis was waived.

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