



Survival benefit and toxicity profile of adjuvant icotinib for patients with *EGFR* mutation-positive non-small cell lung carcinoma: a retrospective study

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Background: Adjuvant *epidermal growth factor receptor* (*EGFR*) tyrosine kinase inhibitors (TKIs) are increasingly considered for the tailored management of resectable non-small cell lung cancer (NSCLC). This study aimed to analyze the survival and toxicity profile of patients with *EGFR* mutation-positive NSCLC treated with adjuvant icotinib.

Methods: This was a single-center retrospective study of patients with *EGFR* mutation-positive NSCLC who underwent R0 (microscopically margin-negative) resection and received adjuvant icotinib between November 2011 and December 2017. The outcomes included 2-year disease-free survival (DFS) rate, 3-year overall survival (OS) rates, DFS, OS, and adverse events (AEs).

Results: A total of 86 patients receiving adjuvant icotinib were included. Their mean age was 59.7±10.0 years, and 26 (30.2%) patients were male. The 2-year DFS rate was 86.7%, and the 3-year OS rate was 95.3% with adjuvant icotinib. DFS ($P=0.044$) and OS ($P=0.003$) are better in stage I/II disease than in stage III disease. There seems no differences in DFS and OS between patients with low or high preoperative CEA levels (cutoff of 5 ng/mL), patients with exon 19 or 21 *EGFR* mutation or patients with or without smoking history. The most common AEs with adjuvant icotinib were rash (83.7%) and diarrhea (19.8%). One (1.2%) patient-reported grade ≥ 3 AEs. No treatment-related death occurred.

Conclusions: For patients with *EGFR* mutation-positive NSCLC, adjuvant icotinib might be associated with a promising survival benefit, with an acceptable toxicity profile.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor mutation (EGFR mutation); icotinib; adjuvant

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Introduction

Non-small cell lung cancer (NSCLC) accounts for 85–90% of all lung cancers (1). In the United States, the annual incidence of NSCLC is 75 per 100,000 men and 53.5 per 100,000 women; mortality is 55.9 per 100,000 men and 36.3 per 100,000 women (2). In China, the age-standardized incidence of NSCLC is 190.63 per 100,000 individuals, and the age-standardized mortality is 106.98 per 100,000 individuals (3).

The management of early NSCLC requires a multidisciplinary approach (4) with complete surgical resection being the mainstay of treatment (5-8). Whilst platinum based adjuvant chemotherapy improves overall survival (OS) in stage II–IIIA (9-15), treatment related toxicities can affect the quality of life and long-term survival benefits are often minimal (16-18).

More recently, the use of adjuvant *epidermal growth factor receptor* (*EGFR*) tyrosine kinase inhibitor (TKI) such as gefitinib, erlotinib or osimertinib, was reported to improve progression free survival in resected NSCLC harboring mutations in *EGFR* exon 19 and 21, and its use is associated with easier administration and a more favorable toxicity profiles when compared to chemotherapy (19-22). For example, the ADJUVANT/CTONG1104 trial showed for the first time *EGFR*-TKI adjuvant therapy resulted in a higher 3-year disease-free survival (DFS) rate compared with cisplatin-based adjuvant chemotherapy in patients with completely resected stage II–IIIA (N1-N2) *EGFR* mutation-positive NSCLC (39.6% *vs.* 32.5%; $P=0.316$) (23). However, a recent meta-analysis revealed a PFS benefit of gefitinib or erlotinib compared with chemotherapy in patients with *EGFR* mutation-positive, but there was no OS benefit (24). A retrospective study showed that, compared with no *EGFR*-TKI treatment, adjuvant erlotinib or gefitinib can improve the 2-year DFS rate of patients with resected lung adenocarcinoma harboring *EGFR* exon 19 or 21 mutations (89% *vs.* 72%; $P=0.06$) (21). In September 2020, the latest results of ADAURA phase 3 trial of osimertinib *vs.* placebo after resection of non-squamous IB–IIIA NSCLC was reported (20). The results showed that

the 2-year DFS rate of osimertinib group were higher than that of the placebo control group (89% *vs.* 52%); and the DFS hazard ratio (HR) of the two groups was 0.20 (99.12% CI: 0.14–0.30; $P<0.001$).

For the treatment of advanced NSCLC in second-line setting and beyond icotinib was proven to similarly efficacious but safer than gefitinib (25,26). The recent CONVINCENCE trial showed that icotinib could be used as a first-line agent for patients with *EGFR*-positive stage IIIB/IV NSCLC (27), but there is currently insufficient data for its use in the adjuvant setting. A retrospective study of adjuvant icotinib revealed it has survival benefits in R0 NSCLC with *EGFR* mutations with acceptable toxicity (28), but a trial of adjuvant icotinib + chemotherapy *vs.* chemotherapy showed no DFS benefit of adding icotinib to chemotherapy (29). The exploration of such approach is important since adjuvant *EGFR*-TKIs are considered part of a new era for the tailored management of resectable NSCLC (30); importantly since the benefits of adjuvant *EGFR*-TKIs may be variable among different patient subset, data are required to refine patient selection in order to maximize the clinical benefit of such approach.

The present study aimed to examine the survival and toxicity profile of patients with *EGFR* mutation-positive NSCLC treated with adjuvant icotinib. The previous data can provide comparison and reference for our research. Therefore, in view of the difficulty of collecting strictly matched cases, we designed this study without a comparative arm. The results could provide insights into the management of selected patients with NSCLC.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-1214>).

Methods

Study design and patients

Our study was a retrospective analysis of patients with *EGFR* mutation-positive NSCLC who underwent R0 (microscopically margin-negative) resection and received

adjuvant icotinib at the Thoracic Oncology Department of the Tianjin Cancer Hospital between November 2011 and December 2017. ADx-ARMS *EGFR* Five Mutations Detection Kit (Amoy Diagnostics, Xiamen, China) was used to test *EGFR* mutations. All patients who received icotinib treatment and included in this study were patients who were *EGFR*-TKI benefit population (*EGFR*-sensitive mutation-positive). Patients with negative or resistant *EGFR* mutations (such as T790M mutation) were excluded. The inclusion criteria were: (I) age ≥ 18 years; (II) pathologically confirmed diagnosis of stage IB-III B NSCLC and R0 resection (the following risk factors were required for stage IB patients: vascular invasion, visceral pleura involvement, solid or micropapillary components in invasive adenocarcinoma $\geq 30\%$, or dissemination within the airway); (III) no previous history of chemotherapy, radiotherapy, or targeted therapy; (IV) icotinib was started within eight weeks postoperatively, and there were no signs of tumor recurrence before starting the adjuvant therapy; (V) adequate functions of the hematological system, liver, and kidney; (VI) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and (VII) postoperative survival > 3 months.

The exclusion criteria were: (I) history of any cancer other than NSCLC [except for cervical carcinoma in situ, cured basal cell carcinoma, or bladder epithelial tumors (including Ta and Tis)] within 5 years before the adjuvant therapy; (II) history of previous interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis requiring steroid therapy, or any clinically documented active interstitial lung disease, or idiopathic pulmonary fibrosis; (III) partially controlled eye inflammation or eye infection, or any condition that may cause the above-mentioned eye diseases; (IV) any unstable systemic disease, including active infection, uncontrolled hypertension, unstable angina, angina that has started within the last 3 months, congestive heart failure (New York Heart Association grade \geq II), myocardial infarction (within 6 months), severe arrhythmia, or liver, kidney or metabolic diseases requiring medications; (V) human immunodeficiency virus infection; (VI) pregnant or lactating women; or (VII) history of previous neurological or mental disorders, including epilepsy or dementia.

The demographic and clinical characteristics of all patients were extracted from their medical records. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee

approved this study of the Tianjin Cancer Hospital (No. bc2019078). Adjuvant icotinib was used only after a comprehensive discussion between the patient and the physicians, and after tumor board discussion. The patients provided informed consent before receiving adjuvant icotinib.

Adjuvant therapy

R0 resection was achieved for all patients. Patients received adjuvant icotinib (125 mg, tid, orally) (Betta Pharmaceuticals Co., Ltd., Zhejiang, China) for 2 years. The medication was withdrawn if there was disease recurrence or intolerable toxicities. Any other postoperative combined therapies were recorded.

Outcomes and follow-up

Patients were followed routinely every 3 months. The outcomes included the 2-year DFS rate, 3-year OS rates, DFS, OS, and adverse events (AEs). Subgroup DFS and OS analyses were conducted with disease stages, preoperative carcinoembryonic antigen (CEA) levels, history of smoking, and *EGFR* mutation. DFS was defined as the time from surgery to disease recurrence or all-cause death, whichever occurred first. The OS was defined as the time from surgery to all-cause death. AEs were reported and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables are expressed as means \pm standard deviation (SD). Categorical variables are expressed as frequency (percentage). Patient DFS and OS were plotted using the Kaplan-Meier curve and compared using the log-ranking test. $P < 0.05$ was considered statistically significant. The minimal *post-hoc* power was defined as 60%.

Results

Characteristics of the patients

Table 1 presents the characteristics of the 86 patients receiving adjuvant icotinib. Their mean age was 59.7 ± 10.0 years, and 26 (30.2%) patients were male. All patients had an ECOG performance status of 0. Most patients had lung adenocarcinoma

Table 1 Demographic and clinical characteristics

Variable	Icotinib (n=86)
Age (years), mean ± SD	59.7±10.0
Male, n (%)	26 (30.2)
Smoking, n (%)	25 (29.1)
Histology, n (%)	
Adenocarcinoma	81 (94.2)
Squamous cell carcinoma	3 (3.5)
Adenosquamous carcinoma	1 (1.2)
Signet ring cell carcinoma	1 (1.2)
Comorbidity, n (%)	
Hypertension	28 (32.6)
Coronary heart disease	7 (8.1)
Diabetes mellitus	8 (9.3)
Myocardial ischemia	5 (5.8)
Hypothyroidism	4 (4.7)
Type of resection, n (%)	
Lobectomy	67 (77.9)
Bilobectomy	15 (17.4)
Segmentectomy	1 (1.2)
Sleeve pneumonectomy	2 (2.3)
Total pneumonectomy	1 (1.2)
TNM stage, n (%)	
IB	46 (53.5)
IIA	3 (3.5)
IIB	5 (5.8)
IIIA	24 (27.9)
IIIB	8 (9.3)
T stage, n (%)	
T1	1 (1.2)
T2	69 (80.2)
T3	6 (7.0)
T4	10 (11.6)
N stage, n (%)	
N0	57 (66.3)
N1	2 (2.3)
N2	27 (31.4)

Table 1 (continued)

Table 1 (continued)

Variable	Icotinib (n=86)
Preoperative CEA (ng/mL), n (%)	
≤5	63 (73.2)
>5	22 (25.6)
Unknown	1 (1.2)
EGFR mutation, n (%)	
Exon 18	2 (2.3)
Exon 19	40 (46.5)
Exon 20	1 (1.2)
Exon 21	42 (48.8)
Exon 19 and 21	1 (1.2)
Postoperative CEA (ng/ml), n (%)	
≤5	69 (80.2)
>5	6 (7.0)
Unknown	11 (12.8)
Postoperative combined treatment, n (%)	
Chemotherapy	5 (5.8)
Radiotherapy	13 (15.1)

CEA, carcinoembryonic antigen; *EGFR*, epidermal growth factor receptor; SD, standard deviation.

[81 (94.2%)], T2 disease [69 (80.2%)], N0 disease [57 (66.3%)], preoperative CEA ≤5 ng/mL [63 (73.2%)], and underwent lobectomy [67 (77.9%)]. The *EGFR* mutations were: exon 18 (n=2, 2.3%), exon 19 (n=40, 46.5%), exon 20 (n=1, 1.2%), exon 21 (n=42, 48.8%), and compound exon 19 & 21 mutation (n=1, 1.2%). In addition to adjuvant icotinib, 5 (5.8%) and 13 (15.1%) patients received postoperative chemotherapy and radiotherapy, respectively.

Survival

The median follow-up time was 48 months. Most patients (93%) had a follow-up period of more than 3 years. *Figure 1* presents the survival data of patients receiving adjuvant icotinib. The median DFS and OS were not reached. The 2-year DFS rate and the 3-year OS rate was 86.7% and 95.3%, respectively.

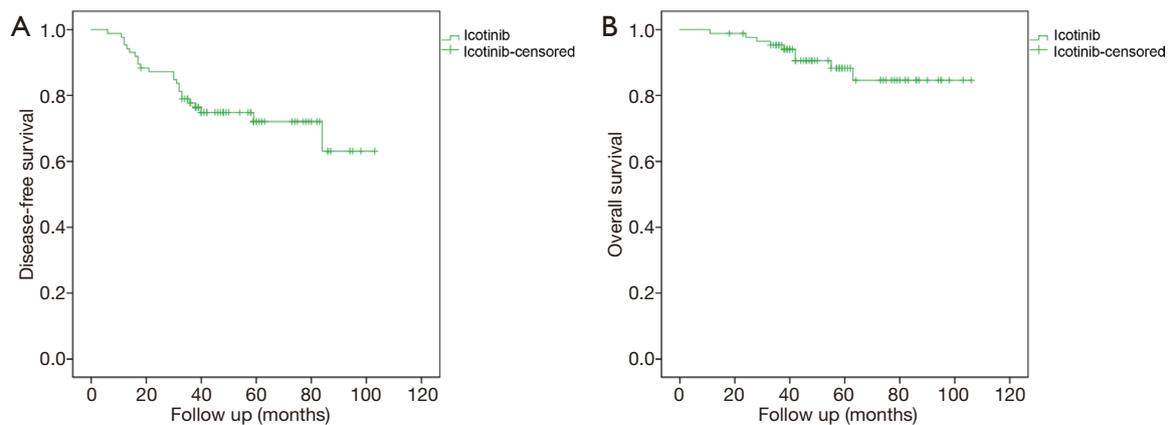


Figure 1 Kaplan-Meier curves of patients receiving adjuvant icotinib. (A) Disease-free survival. (B) Overall survival.

Subgroup analysis

We excluded patients who had received combined postoperative therapy and performed a subgroup analysis. The results showed that DFS ($P=0.044$) and OS ($P=0.003$) is better in stage I/II disease than in stage III disease (Figure 2). Specifically, DFS ($P=0.041$) and OS ($P=0.007$) is better in T1–2 disease than in T3–4 disease. N0 disease had better DFS ($P=0.016$), and a better trend of OS ($P=0.061$) was found compared with N1–2 disease (Figure S1). There seems no differences in DFS and OS between patients with low or high preoperative CEA levels (cutoff of 5 ng/mL), patients with exon 19 or 21 *EGFR* mutation or patients with or without smoking history (Figure 2). However, as some subgroup numbers are small (especially after we excluded patients with combined treatment), we calculated the post-hoc power of all subgroup analyses, and the power is low (<60%). Thus, we cannot draw the conclusions that there is no difference in DFS or OS between those groups as this study are not powered to answer. However, all these statistical results in this study may provide some hints for future research, and these results need to be verified by future studies with larger sample sizes.

AEs

AEs are shown in Table 2. Of the patients who received adjuvant icotinib, 73 (84.9%) had grade 1–2 AEs, and one (1.2%) had grade 3 AEs. Among them, 72 (83.7%) had a rash, 17 (19.8%) developed diarrhea, 4 (4.7%) had elevated transaminases, 5 (5.8%) experienced fatigue (including one grade 3 fatigue), 4 (4.7%) had oral ulcers, and 1 (1.2%) had nausea. Most AEs were relieved without any

treatment. Patients without spontaneous relief were treated symptomatically, and no severe AEs, including interstitial lung disease, occurred. Multiple AEs were observed in 24 (32.9%) patients.

Discussion

EGFR-TKIs have been approved by Food and Drug Administration and Chinese National Medical Products Administration for use in the treatment of advanced NSCLC patients who cannot be surgically resected, and the efficacy of *EGFR*-TKIs were usually better than that of chemotherapy or no treatment (31). A meta-analysis showed that, in advanced NSCLC, the median survival time was 13.26, 13.52, and 12.58 months for gefitinib, erlotinib and icotinib, respectively (25). Icotinib has similar efficacy than gefitinib but a more favorable safety profile when used as a second- or further-line therapy in patients with advanced NSCLC (25,26), but there is currently insufficient data for icotinib as adjuvant therapy in patients with *EGFR* mutation-positive NSCLC (27). *EGFR*-TKIs are considered part of a new era for the tailored management of resectable *EGFR* mutation-positive NSCLC (30), and our results suggest that the use of adjuvant icotinib in such cohort might be associated with a promising survival benefit with an acceptable toxicity profile.

It has been well documented that adjuvant platinum based chemotherapy improves the survival in patients with resected NSCLC (9–12), but chemotherapy-related AEs and treatment related mortality were reported (9). More recently, adjuvant gefitinib, erlotinib and osimertinib have shown improvement in PFS in resected stage I–III NSCLC with *EGFR* exon 19 and 21 mutations (20–22). Compared

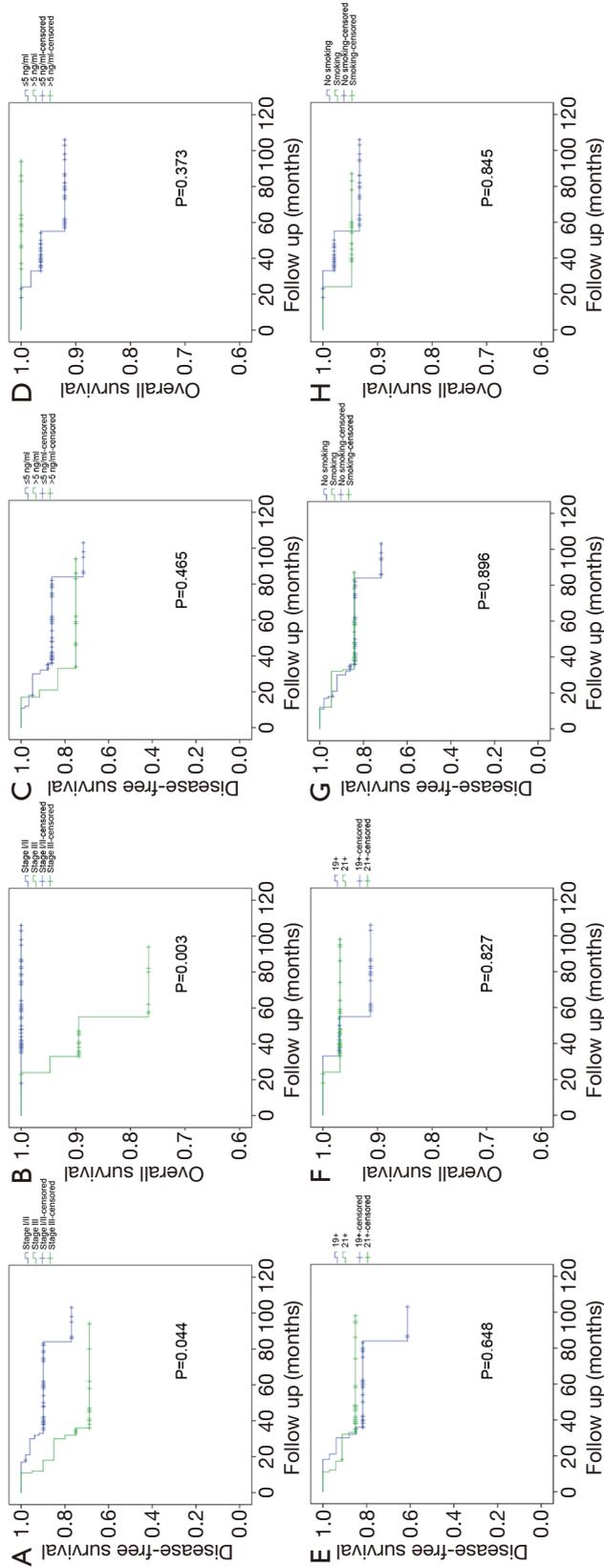


Figure 2 Kaplan-Meier curves for the subgroup analyses in patients receiving adjuvant icotinib. Subgroup DFS (A) and OS (B) curves based on overall TNM stage (I/II vs. III); subgroup DFS (C) and OS (D) curves with preoperative carcinoembryonic antigen level (≤ 5 vs. >5 ng/mL); subgroup DFS (E) and OS (F) curves for epidermal growth factor receptor mutation (19 vs. 21); and subgroup DFS (G) and OS (H) curves for the history of smoking (yes vs. no). DFS, disease-free survival; OS, overall survival.

Table 2 Adverse events

The event and number (%)	Icotinib (n=86)		
	Grades 1–2	Grade 3	Grade 4
Any adverse event	73 (84.9)	1 (1.2)	0
Rash	72 (83.7)	0	0
Diarrhea	17 (19.8)	0	0
Fatigue	4 (4.7)	1 (1.2)	0
Elevated ALT/AST	4 (4.7)	0	0
Oral ulcers	4 (4.7)	0	0
Nausea	1 (1.2)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

with gefitinib, icotinib has similar efficacy, but a better safety profile (25,26), and the CONVINCe trial showed better outcomes of the first-line icotinib *vs.* chemotherapy for stage IIIB-IV NSCLC (27). A retrospective study of adjuvant icotinib revealed it has survival benefits in R0 NSCLC with *EGFR* mutations with acceptable toxicity (28). In most *EGFR* adjuvant trials, there is the problem of the lacking OS data as well the problem regarding the treatment duration. The lack of OS data may be due to insufficient follow-up time and insufficient number of events, in which condition, OS data may be unreliable therefore have not been displayed. Follow-up data of these clinical trials can be collected and updated in the future. At ASCO 2020, the OS data of ADJUVANT was revealed, showing that the median OS of patients receiving adjuvant gefitinib was 75.5 months, which was nearly 13 months longer than the 62.8 months in the adjuvant chemotherapy group (HR: 0.92; 95% CI: 0.62–1.36; P=0.674) (32). Treatment duration is also an issue that have not been concluded. Current *EGFR*-TKI adjuvant trials differ in the choice of treatment duration. Regarding the exploration of treatment duration, some studies have been carried out, we look forward to the results of those studies. In present study, two years was adopted as treatment duration and the DFS/OS data was shown.

The present study showed that the 2-year DFS rate was 86.7% and the 3-year OS rate was 95.3%, which are better than the historical survival data with chemotherapy (2-year DFS of 57–76%, 3-year OS of 62–74%) or with no treatment (2-year DFS of 47–60%, 3-year OS of 57–72%) (9–12), suggesting a possible better survival benefit for adjuvant icotinib targeted therapy compared with adjuvant chemotherapy. The median DFS and OS were not reached

in the present study. These results might be associated with excellent baseline characteristics of the patients since about 50% of the patients were stage IB, and the ECOG performance status was 0 in all patients. These findings suggest that adjuvant therapy with icotinib is feasible and might result in an excellent prognosis in patients with stage IB–IIIB NSCLC.

Further subgroup analysis showed that both DFS and OS were better for stage I/II disease than for stage III and T1–2 disease compared with T3–4. DFS was better for N0 tumors than for N1–2. Those results are in agreement with the recognized prognostic factors of NSCLC (4,8).

In the present study, the most common AEs in the icotinib group were rash and diarrhea, with acceptable tolerability. Spontaneous relief was observed in most patients, and no severe AEs, including interstitial lung disease, occurred. If interstitial pneumonia occurs, the treatment mainly includes: stop taking *EGFR*-TKI immediately; clinical treatment strategies are mainly symptomatic and supportive treatment: oxygen inhalation, anti-inflammatory, anti-infective, and anti-fibrotic treatments. Previous studies of icotinib already revealed its favorable safety profile (25–27,33). However, in terms of some specific side effects, some other *EGFR*-TKIs may have less side effects. For example, clinical trials (27,34,35) showed that although icotinib has the lowest overall incidence of diarrhea, many other *EGFR*-TKIs have a lower incidence of grade ≥ 3 diarrhea. In addition, compared with icotinib, osimertinib has a lower incidence of drug-induced liver injury, gefitinib and osimertinib have a lower incidence of grade ≥ 3 rash, etc. The results of this study suggest icotinib with a standard dose is suitable for adjuvant therapy in patients with R0 resected NSCLC, but further prospective clinical studies must validate this suitability. In clinical practice, we need to select the most suitable *EGFR*-TKI according to the specific situation.

This study has limitations. First, biases are unavoidable in single-center retrospective studies. In the future, we will actively carry out multi-center clinical study in order to obtain more generalized results. Second, multivariate analysis was statistically impractical due to the high censoring rate. Third, this was a single-arm study without a comparator. Furthermore, some issues need to be addressed: (I) whether icotinib monotherapy is enough; (II) the optimal duration of adjuvant icotinib therapy; (III) sequence and timing of adjuvant targeted therapy and chemotherapy; and (IV) optimal target patients. The present study indicated that adjuvant icotinib therapy may prolonged survival with

an acceptable safety profile, Further randomized controlled trials must verify the efficacy and safety of adjuvant therapy with icotinib to support our hypothesis. These trials might further confirm the impact of adjuvant icotinib therapy on DFS and OS and will identify the target population.

Conclusions

This retrospective study suggests that adjuvant icotinib might be associated with a promising survival benefit with an acceptable toxicity profile. The OS rate observed in this study was higher than that reported in the literature for chemotherapy. These results are essential because *EGFR*-TKIs are considered central to the modern tailored management of resectable NSCLC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/tlcr-20-1214>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/tlcr-20-1214>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tlcr-20-1214>). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee approved this study of the Tianjin Cancer Hospital (No. bc2019078). The patients provided informed consent before receiving adjuvant icotinib.

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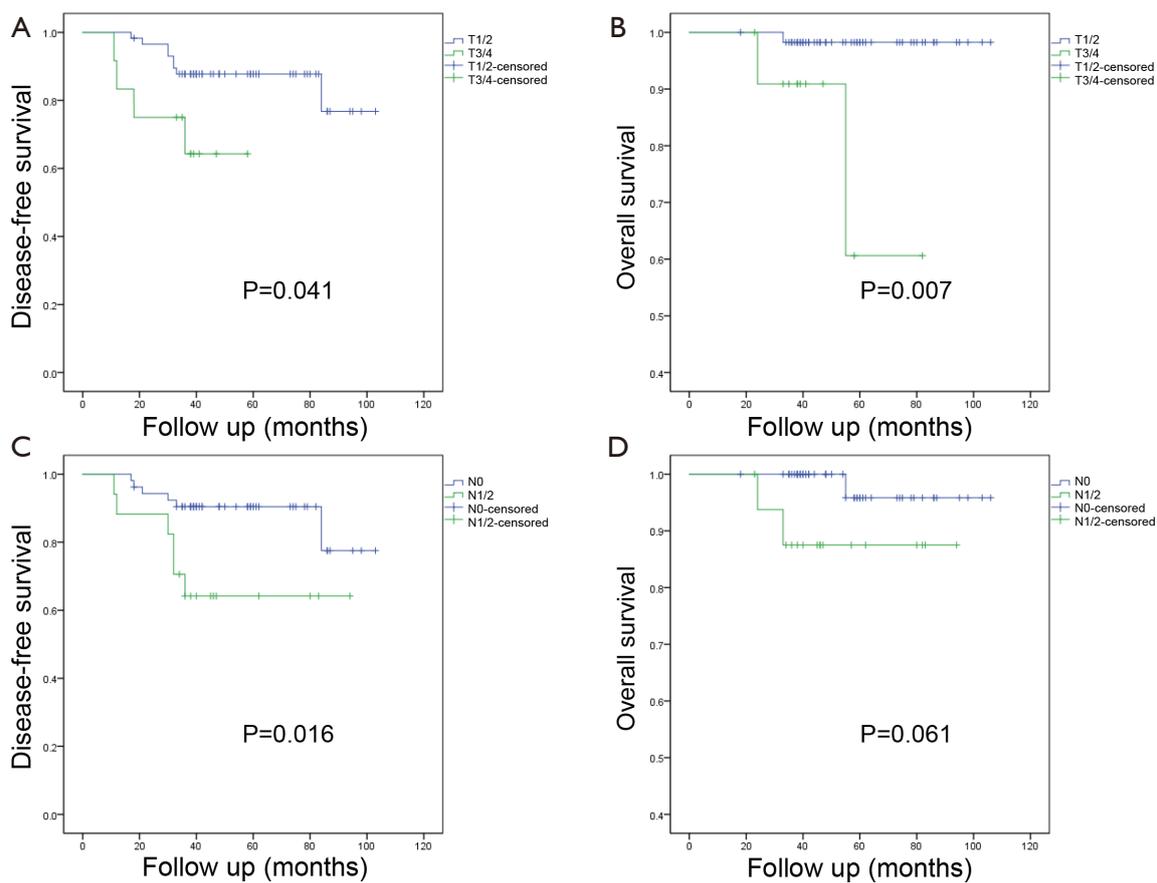


Figure S1 Kaplan-Meier curves for the subgroup analyses in patients receiving adjuvant icotinib. Subgroup DFS (A) and OS (B) curves with T stage (T1/2 *vs.* T3/4); and subgroup DFS (C) and OS (D) curves with N stage (N0 *vs.* N1/2). DFS, disease-free survival; OS, overall survival.