ORIGINAL ARTICLE

An Observational Study on Treatment Outcomes in Patients With Stage III NSCLC in Taiwan: The KINDLE Study

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ABSTRACT

Introduction: Patients with stage III NSCLC represent a very heterogenous group that requires different treatment strategies, especially in patients with N2 (2 nearby lymph nodes having cancer)-positive NSCLC and unresectable *EGFR*-mutant NSCLC. This real-world study may provide more insights into treatment decisions.

Methods: The KINDLE study is a large, multinational real-world observational study that assessed different treatment strategies in patients with stage III NSCLC. Progression-free survival (PFS) and overall survival (OS) were estimated and compared using Kaplan-Meier and log-rank testing. Patients were classified on the basis of disease stage, resectability, and treatment modalities.

Results: The Taiwan subgroup enrolled 200 patients. The median PFS and OS values were similar among patients with stage IIIA and stage IIIB disease, but were significantly better in patients who were deemed as a resectable disease than in those who were deemed as an unresectable disease. In patients with N2-positive NSCLC, patients who underwent surgery had better PFS, but not OS, than patients

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administered with chemoradiotherapy (CRT) (PFS 13.4 vs. 7.3 mo, hazard ratio [HR] = 0.18, $p < 0.001$; OS 32.4 vs. 22.0 mo, HR = 0.64, $p = 0.215$). Among patients with unresectable *EGFR*-mutant NSCLC, OS was significantly poorer after upfront EGFR–tyrosine kinase inhibitors (TKI) than after upfront CRT with sequential EGFR-TKI (27.4 vs. 49.0 mo, HR = 3.09, $p = 0.03$).

Conclusions: Our study suggests that surgery could be added as part of therapy for patients with stage III N2-positive NSCLC. Moreover, upfront CRT with sequential EGFR-TKI seems to be appropriate for stage III unresectable *EGFR*-mutant NSCLC. Further randomized studies are needed to validate these results.

Keywords: Stage III non-small cell lung cancer; N2-positive disease; Epidermal growth factor receptor mutation; Chemoradiotherapy; Tyrosine kinase inhibitors

Introduction

Stage III NSCLC comprises approximately one-fifth of patients who have lung cancer; and its clinical outcomes remain dismal, with 5-year survival rates of 10% to 20%.[1–3] Patients with stage III NSCLC represent a very heterogenous group with diverse tumor and nodal status, and treatment options,[4,5] which vary from patients with resectable disease undergoing surgery to patients with unresectable disease receiving consolidative chemoradiotherapy (CRT).[6] However, the criteria for selecting treatment differ among guidelines, especially in nonbulky ipsilateral disease and subcarinal mediastinal lymphatic involvement (N2) disease.[7] The Intergroup study (INT 0139) comparing the efficacy between definitive CRT and CRT followed by surgery in patients with stage III N2-positive NSCLC reported a significantly improved progression-free survival (PFS) in patients receiving CRT followed by surgery (12.8 versus 10.5 mo, $p = 0.017$), whereas the overall survival (OS) seemed to be comparable (23.6 versus 22.2 mo, $p = 0.240$).[8] The ESPATUE trial also reported similar results, the median OS being similar among patients receiving definitive CRT and those receiving CRT followed by surgery.[9] Thus, the role of surgery in patients with stage III N2-positive NSCLC remains controversial. In the current study, we used real-world evidence to understand the diverse practice patterns and treatment pathways, which may gain disease insights and enable clinicians to make optimum clinical judgments.[10]

In the randomized phase III PACIFIC study of consolidation therapy with durvalumab versus placebo in patients with stage III NSCLC whose disease had not progressed after completing concurrent CRT, median PFS was significantly prolonged with durvalumab (16.8 mo vs. 5.6 mo, $p < 0.001$)[11] and the 5-year survival rate also favored durvalumab (42.9% vs. 33.4%).[12] However, only 6.0% of patients in the PACIFIC study had *EGFR* mutations. In a meta-analysis, which reported that immune checkpoint inhibitors did not improve OS in *EGFR*-mutant NSCLC,[13] there was a high possibility that durvalumab as consolidation therapy may not be beneficial for patients with *EGFR*-mutant stage III NSCLC after completion of concurrent CRT. Moreover, two previous studies have revealed that patients with *EGFR* mutation may have a shorter PFS after completing concurrent CRT.[14,15] Although CRT is associated with better locoregional control, most patients with *EGFR* mutations experience disease progression with distant metastasis,[16,17] including brain metastasis.[18] Given the better PFS and objective response rates provided by treatment with EGFR–tyrosine kinase inhibitors (TKIs)[13] and limited data of immunotherapy consolidation in patients harbored *EGFR* mutation,[12] the role of upfront concurrent CRT in patients with stage III unresectable *EGFR*-mutant NSCLC needs to be reevaluated.

In this study, we have analyzed the subgroup of patients in the Taiwan arm of the KINDLE study. Survival outcomes of patients with stage III NSCLC are analyzed and compared among different subgroups. Patients were classified on the basis of disease stage and resectability. Treatment outcomes of surgery, chemotherapy, or CRT were analyzed in patients without *EGFR* mutations. Finally, in those with *EGFR* mutations, treatment outcomes were analyzed for patients given upfront CRT with subsequent EGFR-TKIs at progression and those given upfront EGFR-TKIs without CRT.

Materials and Methods

Patient Population

The KINDLE study is a multinational, real-world study that retrospectively reviewed treatment strategies used in patients with stage III NSCLC diagnosed between January 1, 2013 and December 31, 2017.[19] Patients aged younger than 18 years, with concomitant cancer occurring within 5 years of stage III NSCLC diagnosis (except for nonmetastatic nonmelanoma skin cancers, or in situ or benign neoplasms), or with a follow-up period shorter than 9 months were excluded. Sociodemographic characteristics, including age, sex, body mass index, ethnicity, smoking status, and asbestos exposure, were recorded. Clinical characteristics were also extracted and included TNM staging according to

American Joint Committee on Cancer, seventh edition at diagnosis, pathological findings, *EGFR* mutation status, the disease resectability on the basis of multidisciplinary team discussion, Eastern Cooperative Oncology Group (ECOG) performance score, and comorbidities. Treatment strategies and timing of treatment modalities were also recorded for each patient, including systemic therapy and radiotherapy. All patients were followed until death or December 31, 2018. Clinical demographics and treatment patterns were summarized by descriptive statistics.

PFS and OS Analyses

The median PFS and OS for all patients were estimated by Kaplan-Meier method and reported with two-sided 95% confidence intervals (CIs). PFS was calculated from the date of initiation of first-line treatment for stage III NSCLC to disease progression after treatment or tumor recurrence after surgery. Given the retrospective nature of the present study, the disease progression or recurrence was determined through the medical records of progressive disease according to pathological findings, image studies, or treating physician's statement. OS was calculated from the date of diagnosis to the date of death. PFS and OS were compared between patients with stage IIIA and stage IIIB disease, and between patients with resectable and unresectable disease, using the log-rank test. First-line treatment strategies on the basis of different disease stages or resectability status were also recorded.

Subgroup Analyses

In the first subgroup survival analysis, PFS and OS were compared using the log-rank test among patients receiving different treatment modalities, including surgery (including perioperative therapy), chemotherapy alone, and CRT (either sequential or concurrent). The subgroup analysis of patients with N2-positive NSCLC was also performed to compare the efficacy between surgery and CRT. The second subgroup survival analysis enrolled patients with unresectable *EGFR*-mutant NSCLC who received upfront CRT or upfront EGFR-TKI as the first-line therapy. To evaluate the association of *EGFR* mutations with treatment outcomes, patients with unresectable *EGFR* wild-type NSCLC receiving CRT were also enrolled. The patients were classified into three groups, including patients with wild-type *EGFR* receiving CRT as the first-line therapy (group 1), patients with *EGFR* mutation receiving upfront EGFR-TKIs (group 2), and patients with *EGFR* mutation receiving upfront CRT with sequential EGFR-TKIs after disease progression (group 3). PFS and OS were also compared using the log-rank test among patients in different groups. As patients in group 3 received EGFR-TKIs for disease progression after CRT, PFS2 was also calculated from the date of initiation of CRT therapy to the date of disease progression after the use of EGFR-TKIs for patients in group 3. For patients in groups 1 and 2, PFS2 was the same as PFS (Supplementary Fig. 1).

Statistical Analysis

Frequency distributions and descriptive statistics were calculated for the demographic and clinical variables. Categorical variables were compared using the chi-square test or Fisher's exact test, whereas continuous variables were compared using the *t* test or the Wilcoxon ranked sum test. Cox proportional hazards regression with propensity score analysis was performed for PFS, PFS2, and OS. The propensity scoring analysis was conducted with the stabilized inverse probability of treatment weighting (IPTW) method, which was adjusted by the designated factors including age, sex, T stage, N stage, and performance status. The selection of possible predictors and determinants was on the basis of previous studies investigating the prognostic factors of survival in lung cancer. Age, sex, tumor stage, nodal stage, and performance status were chosen as the predictors and prognostic factors. Statistical Analysis System software version 9.4 (SAS Institute, Cary, NC) was used to perform the analyses. All the reported *p* values are two-sided.

Results

Characteristics of Patients

The KINDLE study Taiwan subgroup enrolled a total of 200 patients. The baseline characteristics for the entire cohort are summarized in Supplementary Table 1. The mean age of the patients was 64 years old (interquartile range [IQR]: 56–73), with 71 men (35.5%) and 129 women (64.5%). There were 90 patients (45.0%) who had stage IIIA disease and 110 patients (55.0%) who had stage IIIB disease. Most patients had adenocarcinoma (61.0%), followed by squamous cell carcinoma (29.0%) and other histologic subtypes. Around half of patients were never-smokers (46.5%) and had no asbestos contact history (49.5%). Classification of patients by resectability identified 56 (28.0%) with resectable disease and 125 (62.5%) with unresectable disease; resectability was not defined for the remaining 19 patients. Most patients (116 [58.0%]) had good performance status (ECOG score 0–1) before first-line therapy. Approximately one-third (64 patients [32.0%]) had genomic alterations, including 62 patients with an *EGFR* mutation, one patient with an *ALK* rearrangement, and one patient with a *ROS1* rearrangement. After excluding six patients who received only palliative

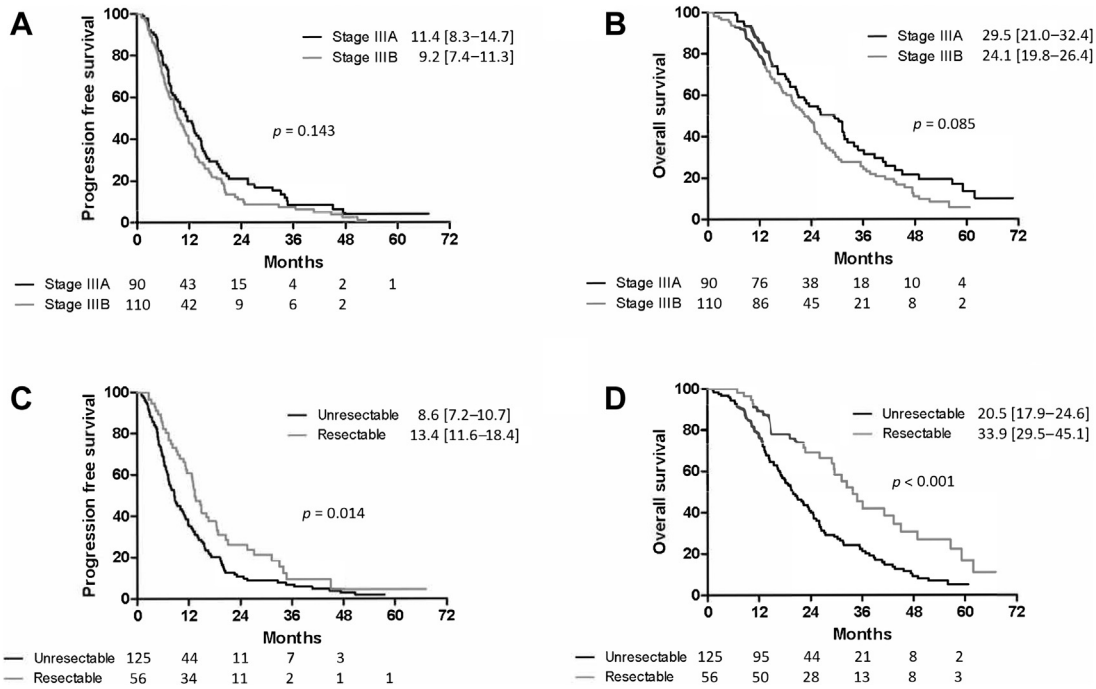

Figure 1. (*A*) Progression-free survival and (*B*) overall survival among patients with stage IIIA and stage IIIB NSCLC. (*C*) Progression-free survival and (*D*) overall survival among patients with resectable and unresectable NSCLC.

radiotherapy or no effective treatment, the remaining patients were classified on the basis of the choice of first-line therapy, including targeted therapy (N = 33), CRT (N = 71), chemotherapy alone (N = 24), and surgery (N = 66). No patients in the CRT group had received consolidation therapy or immunotherapy. Patients who received targeted therapy included 32 patients with *EGFR*-mutant NSCLC treated with EGFR-TKIs and one patient with *ALK*-rearranged NSCLC administered crizotinib. The CRT cohort was further classified as *EGFR*-mutant NSCLC and *EGFR* wild-type NSCLC. Supplementary Figure 2 details the inclusion of subjects for survival analysis.

Treatment Patterns and Survival Analyses

The PFS and OS values for all 200 patients were 10.3 (IQR: 8.8–11.8 mo) and 24.8 (IQR: 21.3–27.4 mo) months, respectively (Supplementary Fig. 3). Patients with stage IIIA or stage IIIB NSCLC had similar median PFS (11.4 vs. 9.2 mo, respectively; log-rank test, $p = 0.143$) and median OS values (29.5 vs. 24.1 mo, respectively; log-rank test, $p = 0.085$) (Fig. 1*A* and *B*). Among the 90 patients with stage IIIA disease, 78 (86.7%) received curative-intent therapy, including 59 (65.6%) who received surgery and 19 (21.1%) who received CRT. In contrast, of the 110 patients with stage IIIB disease, only 59 (53.7%) received curative-intent therapy, including surgery and CRT (Supplementary Table 2).

Patients with resectable disease had significantly better median PFS (13.4 vs. 8.6 mo, respectively; log-rank test, $p = 0.014$) and OS (33.9 vs. 20.5 mo, respectively; log-rank test, $p < 0.001$) than patients with unresectable disease (Fig. 1*C* and *D*). Among 56 patients with resectable disease, all received curative-intent therapy, including 54 patients who underwent surgery and two patients who received CRT. In contrast, of 125 patients with unresectable disease, 74 (59.2%) received curative-intent therapy, including surgery and CRT, and 45 (36.0%) received only systemic therapy (Supplementary Table 2).

Subgroup Analysis

In the first subgroup analysis, patients were classified by different first-line treatment modalities, which included surgery, CRT, and chemotherapy. Patients who were given surgery as first-line therapy had a higher proportion of T1 and T2 stage, less N3 disease, and were mostly stage IIIA disease (Supplementary Table 3). The median PFS in those who underwent surgery was 13.7 months, which was significantly longer than in those receiving CRT-based therapy or chemotherapy alone (log-rank test, $p < 0.001$) (Fig. 2*A*); similarly, the median OS in patients who underwent surgery was 32.4 months, which was also significantly longer than in those receiving CRT-based therapy or chemotherapy alone (log-rank test, $p < 0.001$) (Fig. 2*B*). In a Cox proportional hazard regression analysis using stabilized IPTW

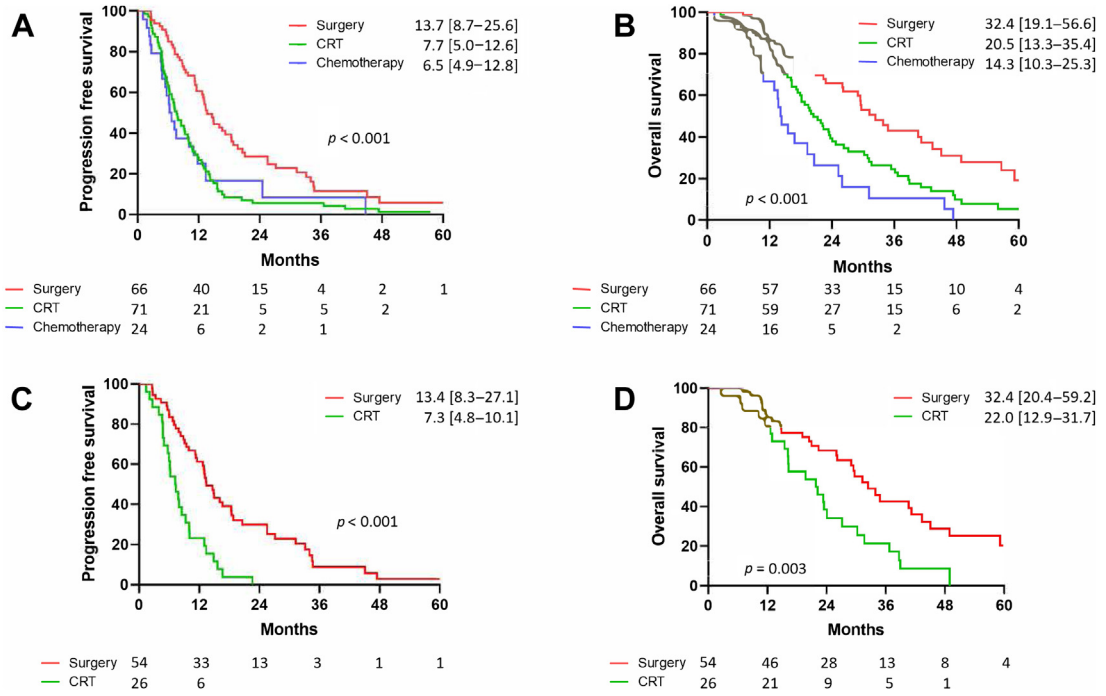

Figure 2. (*A*)Progression-free survival and (*B*) overall survival among patients without an *EGFR* mutation who underwent surgery, CRT, or chemotherapy. (*C*) Progression-free survival and (*D*) overall survival among patients with N2-positive disease who underwent surgery or CRT. CRT, chemoradiotherapy.

method, receipt of surgery was independently associated with a good prognosis for both PFS and OS, with hazard ratios (HRs) of 0.31 (95% CI: 0.18–0.53, $p = 0.001$) and 0.47 (95% CI: 0.27–0.81, $p = 0.007$), respectively (Table 1). The results of Cox proportional hazard regression analysis without propensity score analysis were summarized in Supplementary Table 4. However, the baseline characteristics vary among patients who received different treatment modalities. To better compare treatment efficacies of CRT and surgery, 80 patients with N2-positive NSCLC were also analyzed. This cohort received surgery as first-line therapy and had a median PFS of 13.4 months, which was significantly longer than patients with N2-positive NSCLC who received CRT as first-line therapy (13.4 vs. 7.3 mo, log-rank test, $p < 0.001$) (Fig. 2*C*). Similarly, the median OS was also longer in patients receiving surgery as the first-line therapy than those receiving CRT as the first-line therapy (32.4 vs. 22.0 mo, log-rank test, $p = 0.003$) (Fig. 2*D*). In the Cox proportional hazard regression analysis using stabilized IPTW method, receipt of surgery was an independent good prognostic factor for PFS in patients with N2-positive NSCLC (HR = 0.18, 95% CI: 0.09–0.37, $p < 0.001$), but not for OS (Table 2). The results of Cox proportional hazard regression analysis without propensity score analysis were summarized in Supplementary Table 5. Of the 54 patients with N2-positive NSCLC who received surgery, 47 had resectable disease on the basis of multidisciplinary team discussion and all underwent lobectomy; 49 (90.7%) of them received perioperative chemotherapy, with 16 also received postoperative radiotherapy; 5 (9.3%) of them received postoperative radiotherapy alone.

In the survival analysis of the second subgroup, patients with unresectable *EGFR*-mutant NSCLC and those with *EGFR* wild-type NSCLC receiving CRT were enrolled and classified into three groups: patients with unresectable *EGFR* wild-type NSCLC given CRT (group 1), patients with unresectable *EGFR*-mutant NSCLC given upfront EGFR-TKIs (group 2), and patients with unresectable *EGFR*-mutant NSCLC given upfront CRT (group 3). Patients in group 2 had a relatively higher proportion of patients aged older than 65 years, but the performance status of these patients was similar with patients in other groups (Supplementary Table 6). The median PFS in group 2 was 15.2 months (IQR: 7.3–20.1 mo), which was longer than patients in group 1 (7.7 mo, IQR: 5.0–12.6 mo) and group 3 (7.4 mo, IQR: 3.7–15.5 mo) (log-rank test, $p = 0.024$) (Fig. 3*A*). After disease progression from CRT, all patients in group 3 received EGFR-TKIs as subsequent therapy. The median PFS2 for patients receiving sequential CRT and EGFR-TKIs was 46.3 months, which was significantly longer than PFS2 values for patients given upfront EGFR-TKIs in group 2 and for patients with *EGFR* wild-type NSCLC given CRT (log-rank test, $p < 0.001$) (Fig. 3*B*). Similarly, the median

Table 1. Cox Proportional Hazard Regression Analysis Using Stabilized IPTW of PFS and OS Among Patients With Stage III NSCLC Who Underwent Surgery, CRT, or Chemotherapy

		PFS		OS	
Variables	Control vs. Reference	Hazard Ratio	*p* Value	Hazard Ratio	*p* Value
Age (y)	≥60 vs. <60	0.89 (0.59-1.32)	0.563	1.15 (0.75-1.76)	0.508
Sex	Male vs. female	0.95 (0.63-1.43)	0.817	1.47 (0.93-2.30)	0.092
T stage	T3-4 vs. T1-2	0.60 (0.38-0.91)	0.019	1.09 (0.68-1.73)	0.713
N stage	N3 vs. N0-2	0.71 (0.43-1.15)	0.167	0.70 (0.43-1.14)	0.158
Performance status	ECOG ≥ 2 vs. ECOG ≤ 1	1.10 (0.53-2.22)	0.800	0.82 (0.38-1.71)	0.591
Treatment	Surgery vs. CRT	0.31 (0.18-0.53)	<0.001	0.47 (0.27-0.81)	0.007
	Chemotherapy vs. CRT	1.08 (0.62-1.85)	0.791	1.88 (1.06-3.31)	0.031

CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; OS; overall survival; PFS, progression-free survival.

OS in group 3 was 49.0 months (IQR: 35.4–56.0 mo), which was significantly longer than the median OS values for group 1 (18.8 mo, IQR: 12.9–30.3 mo) and group 2 (27.4 mo, IQR: 24.6–37.7 mo) (log-rank test, $p = 0.002$) (Fig. 3*C*). To evaluate the prognostic factor, we also performed the Cox proportional hazard regression analysis using stabilized IPTW method. Although receipt of EGFR-TKI as first-line therapy (group 2) was an independent good prognostic factor for PFS (HR = 0.43, 95% CI: 0.19–0.98, $p = 0.046$) in patients with *EGFR* mutation (group 2 versus group 3), it became an independent poor prognostic factor for both PFS2 (HR = 2.94, 95% CI: 1.16–7.42 mo, $p = 0.022$) and OS (HR = 3.09, 95% CI: 1.11–8.60 mo, $p = 0.030$) (Table 3). Similarly, the absence of *EGFR* mutation was also an independent poor prognostic factor for OS (HR = 9.26, 95% CI: 3.37–25.4 mo, $p < 0.001$) in patients receiving CRT as the first-line therapy (group 1 versus group 3) (Table 3). The results of Cox proportional hazard regression analysis without propensity score analysis were summarized in Supplementary Table 7.

Discussion

This subgroup analysis of patients from Taiwan participating in the KINDLE study illustrates three key findings. First, patients with resectable disease had better PFS and OS compared with those with unresectable disease. Second, surgery, compared with CRT or chemotherapy, was associated with better PFS in patients with N2 disease. Finally, in patients with an *EGFR* mutation, upfront CRT with sequential EGFR-TKIs seemed to provide better OS than upfront EGFR-TKIs, which was similar to the global KINDLE study.[20]

The role of surgery in patients with stage III NSCLC, especially in those with N2-positive NSCLC, is an important issue of considerable debate.[21] Previous studies have reported comparable outcomes between patients receiving surgery and those receiving CRT. A previous phase 3 trial, RTOG 89-01, reported that patients undergoing surgery after induction chemotherapy have an OS of 19.4 months, similar to that in patients given definitive radiotherapy (17.4 mo).[22] In another randomized controlled study, the median OS was 16.4 and 17.5 months in patients given induction chemotherapy followed by surgery and in patients given CRT, respectively (HR = 1.06, 95% CI: 0.84–1.35).[23] In the current study, patients receiving surgery as the first-line therapy had significantly better PFS and OS compared with those receiving CRT ($p < 0.001$, Fig. 2*A* and *B*). Although surgery seems to be an independent good prognostic factor (Table 2), higher proportions of patients in the surgery group versus those in the CRT or

Table 2. Cox Proportional Hazard Regression Analysis Using Stabilized IPTW of PFS and OS Among Patients With Stage III N2 NSCLC Who Received CRT or Surgery

		PFS		OS	
Variables	Control vs. Reference	Hazard Ratio	*p* Value	Hazard Ratio	*p* Value
Age (y)	≥60 vs. <60	1.00 (0.52-1.93)	0.994	1.12 (0.57-2.19)	0.745
Sex	Male vs. female	0.77 (0.41-1.43)	0.408	1.21 (0.61-2.40)	0.579
T stage	T3-4 vs. T1-2	0.64 (0.33-1.22)	0.180	1.31 (0.66-2.59)	0.436
Performance status	ECOG ≥ 2 vs. ECOG ≤ 1	0.98 (0.27-3.58)	0.981	2.56 (0.67-9.69)	0.168
Treatment	Surgery vs. CRT	0.18 (0.09-0.37)	<0.001	0.64 (0.31-1.29)	0.215

CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; OS; overall survival; PFS, progression-free survival.

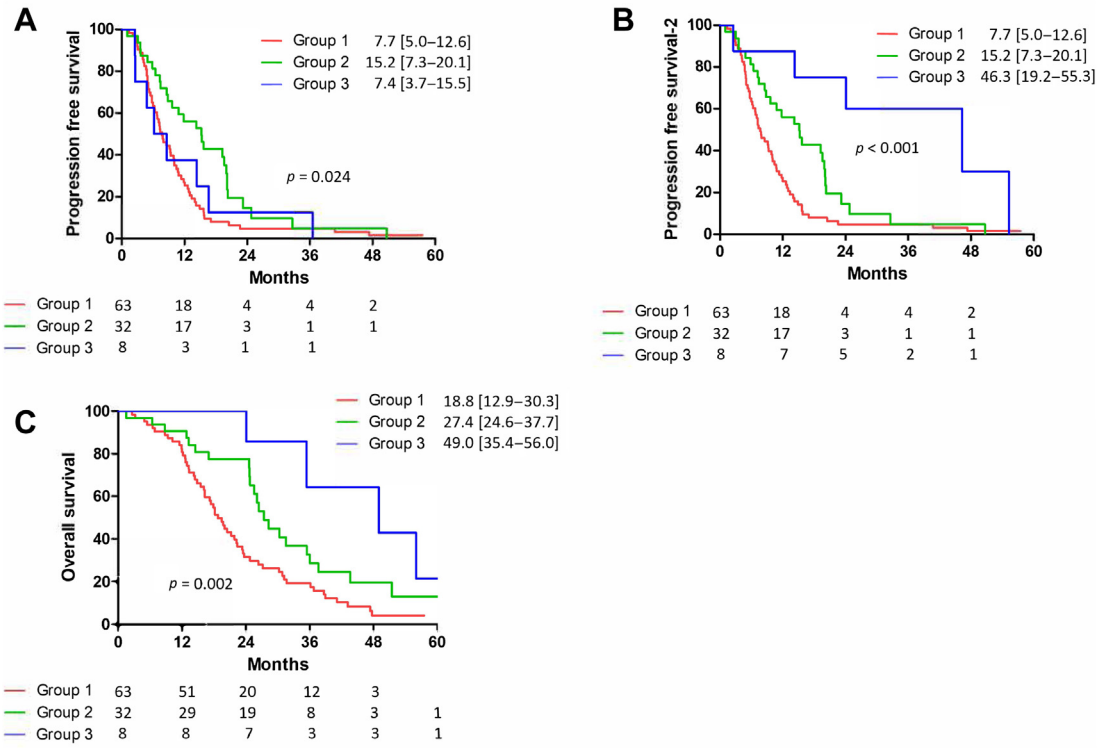

Figure 3. (*A*) Progression-free survival, (*B*) Progression-free survival 2, and (*C*) overall survival among patients with unresectable *EGFR* wild-type NSCLC who were administered CRT and patients with unresectable *EGFR*-mutant NSCLC who were administered upfront CRT or upfront EGFR-TKI. CRT, chemoradiotherapy; TKI, tyrosine kinase inhibitors.

chemotherapy groups had T1 to T2 status and N1 to N2 status. In the subgroup of patients with N2-positive NSCLC, patients in the surgery group had a median OS of 32.4 months, longer than that of patients in the CRT group (22.0 mo) (Fig. 2*D*), although only marginal statistical significance was found after Cox regression analysis (Table 3). The trimodal therapy (combined surgery, chemotherapy, and radiotherapy) and type of surgery may be the reasons for the improvement of OS. Of the 54 patients who underwent surgery in this subgroup analysis, 47 (87.0%) of them had resectable disease and all received lobectomy; 49 (90.7%) of them received perioperative chemotherapy, with 16 patients (29.6%) also receiving postoperative radiotherapy. Although the Intergroup study (INT 0139) failed to exhibit survival benefits of trimodal therapy in the total population, the subgroup of patients receiving lobectomy exhibited marked improved OS.[8] A meta-analysis of data from four trials involving patients given induction chemotherapy followed by surgery and from two trials

Table 3. Cox Proportional Hazard Regression Analysis Using Stabilized IPTW of PFS, PFS2, and OS Among Patients With Stage III Unresectable NSCLC Who Received CRT or Upfront EGFR-TKIs

		PFS		PFS2		OS	
Variables	Control vs. Reference	Hazard Ratio	*p* Value	Hazard Ratio	*p* Value	Hazard Ratio	*p* Value
Age (y)	≥65 vs. <65	1.14 (0.70-1.84)	0.597	1.63 (1.00-2.64)	0.047	2.53 (1.48-4.29)	<0.001
Sex	Male vs. female	0.78 (0.46-1.29)	0.331	1.15 (0.66-1.99)	0.606	1.18 (0.66-2.07)	0.568
T stage	T3-4 vs. T1-2	0.69 (0.40-1.17)	0.174	0.72 (0.40-1.26)	0.246	0.98 (0.53-1.81)	0.959
N stage	N3 vs. N0-2	0.96 (0.59-1.55)	0.881	1.25 (0.76-2.04)	0.377	1.12 (0.65-1.92)	0.674
Performance status	ECOG ≥ 2 vs. ECOG ≤ 1	0.91 (0.42-1.96)	0.807	0.88 (0.40-1.89)	0.738	0.93 (0.40-2.09)	0.853
Treatment	Group 1 vs. Group 3	1.17 (0.54-2.53)	0.688	7.91 (3.05-20.4)	<0.001	9.26 (3.37-25.4)	<0.001
	Group 2 vs. Group 3	0.43 (0.19-0.98)	0.046	2.94 (1.16-7.42)	0.022	3.09 (1.11-8.60)	0.030

Note: Group 1: Patients with *EGFR* wild-type NSCLC received CRT as first-line therapy; Group 2: Patients with *EGFR*-mutant NSCLC received EGFR-TKI as first-line therapy; Group 3: Patients with *EGFR*-mutant NSCLC received CRT as first-line therapy.
CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; OS; overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

including patients given induction CRT followed by surgery pointed out that induction CRT followed by surgery (trimodal therapy) was associated with marginally better OS versus induction chemotherapy followed by surgery (bimodal therapy).[24] Furthermore, a retrospective analysis of the National Cancer Database in patients with stage III N2-positive NSCLC also revealed that patients receiving CRT followed by lobectomy (trimodal therapy) had a significantly longer median OS of 51.4 months than those receiving CRT alone (bimodal therapy) (39.0 mo, $p < 0.001$).[25] Taken together, trimodal therapy may provide clinical benefit to patients with stage III N2-positive NSCLC. Further prospective research is warranted to validate this result.

In Asian patients with advanced-stage NSCLC, approximately 50% harbor an *EGFR* mutation,[26] which is associated with clinical benefit with the use of EGFR-TKI. A meta-analysis of treatment outcomes in *EGFR*-mutant lung cancer has revealed better PFS and objective response rates, with first-generation EGFR-TKIs as compared with chemotherapy.[13] Second-generation EGFR-TKIs afatinib and dacomitinib have exhibited similar survival efficacy in NSCLC,[27,28] whereas the phase III FLAURA study reported that the third-generation EGFR-TKI, simertinib, resulted in better PFS and OS than first-generation EGFR-TKIs[29,30]; and simertinib has become the mainstay of treatment in patients with *EGFR* mutations. A previous database analysis also reported similar median OS between patients with stage III NSCLC receiving upfront CRT and those receiving upfront EGFR-TKIs.[31] In addition, a real-world study evaluating the efficacy of CRT followed by durvalumab consolidation also revealed a short PFS of 7.5 months in patients with *ERBB2* or *EGFR* mutation.[32] Whether the upfront CRT provides clinical benefit in patients with stage III unresectable *EGFR*-mutant NSCLC needs more data to elucidate. Despite two cohort studies comparing the efficacy of CRT between patients with wild-type *EGFR* and those with *EGFR* mutation reporting that the presence of *EGFR* mutation was associated with a shorter PFS,[14,15] the PFS was similar between patients with *EGFR*-mutant and *EGFR* wild-type NSCLC receiving CRT in the present study, which was also similar to the global KINDLE study.[33] Furthermore, although patients with *EGFR* mutation receiving CRT had a shorter PFS (7.4 mo) compared with those with *EGFR* mutation receiving EGFR-TKI (15.2 mo) ($p = 0.024$), the median PFS and OS of patients receiving upfront CRT with sequential EGFR-TKI were 46.3 and 49.0 months, respectively—both of which were markedly longer than the PFS and OS of patients receiving upfront EGFR-TKI. A multi-institutional retrospective study reported that CRT followed by consolidation therapy with EGFR-TKI was associated with a substantially prolonged median PFS (26.1 mo) versus CRT alone (6.9 mo) or CRT followed by consolidation therapy with durvalumab (10.3 mo).[33] This study also highlighted the important role of EGFR-TKI in patients with stage III *EGFR*-mutant NSCLC. Taken together, these data indicate the clinical benefit of upfront CRT and sequential EGFR-TKI therapy, which may result from the potential curative effect of CRT.

Many limitations exist in the current study. First, this study is retrospective, and the basic demographic data were not balanced in each subgroup. However, we used Cox proportional hazard regression analysis with stabilized IPTW to minimize heterogeneity between patients receiving different treatment modalities and revealed similar study results. Second, although staging information was provided, we could not obtain detailed information such as tumor size or the extent of nodal involvement. One study revealed that patients with resected N2 also have varying treatment outcomes, with five-year survival rates ranging from 3% to 34% in patients with minimal N2 disease (one level involved) or multiple-level N2 disease with bulky lymph nodes.[34] The volume of the tumor, in combination with lymph node involvement, may also determine OS.[35] In a subgroup analysis of patients with N2 disease, 47 of 54 patients receiving surgery as first-line therapy were reviewed by a multidisciplinary team and suggested as suitable candidates for surgical resection. The improved outcomes with surgery highlight the evidence suggesting that survival outcomes are better when the multimodality treatment of stage III NSCLC applies the multidisciplinary team approach rather than a traditional care model.[36] Third, although the patients with unresectable *EGFR*-mutant NSCLC exhibited better OS with the upfront CRT therapy, the small number of patients in subgroup survival analysis precludes the definitive conclusions. Although the performance status was similar between patients in these two groups, patients with an *EGFR* mutation who received EGFR-TKI as first-line therapy were relatively older than patients with an *EGFR* mutation receiving CRT as the first-line therapy, which may cause the length time bias. Further prospective randomized study investigations comparing upfront CRT with sequential EGFR-TKIs and upfront EGFR-TKIs in stage III unresectable *EGFR*-mutant NSCLC are warranted to validate this result. Forth, despite we had performed the Cox regression analysis with stabilized inverse propensity treatment weighting, the performance status is still not an independent factor for survival (Table 1 to 3). The possible reason may be the limited number of patients with poor performance status. Among 161 patients in subgroup analysis 1, there are only four patients who had poor performance status (ECOG $\geq$ 2). In addition, patients in subgroup analysis one received surgery, chemotherapy, or CRT as first-line

therapy, which could only be administrated in patients with good performance status. Moreover, among 103 patients in subgroup analysis 2, there are also only nine patients who had poor performance status. Because of the limited number of patients with poor performance status, we could not define the role of performance status in the treatment outcome in the present study.

In conclusion, our study suggests that surgery could be added as part of therapy for patients with stage III N2-positive NSCLC. Moreover, upfront CRT with sequential EGFR-TKI seems to be appropriate for stage III unresectable *EGFR*-mutant NSCLC. Our findings need to be validated with further prospective randomized studies.

CRediT Authorship Contribution Statement

Po-Lan Su: Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing.

Gee-Chen Chang, Shih-Hsin Hsiao, Te-Chun Hsia, Meng-Chih Lin, Min-Hsi Lin, Jin-Yuan Shih, Cheng-Ta Yang, Sheng-Hsiung Yang: Investigation.

Yuh-Min Chen: Conceptualization, Data curation, Investigation, Methodology, Study supervision, Writing - review & editing.

All authors approved the final draft of the submitted manuscript.

Ethics Approval

This study was approved by the institutional review board (IRB) of each participating medical center. Written informed consent was obtained from each patient except those with a waiver granted from the IRB of each medical center.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100292.

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