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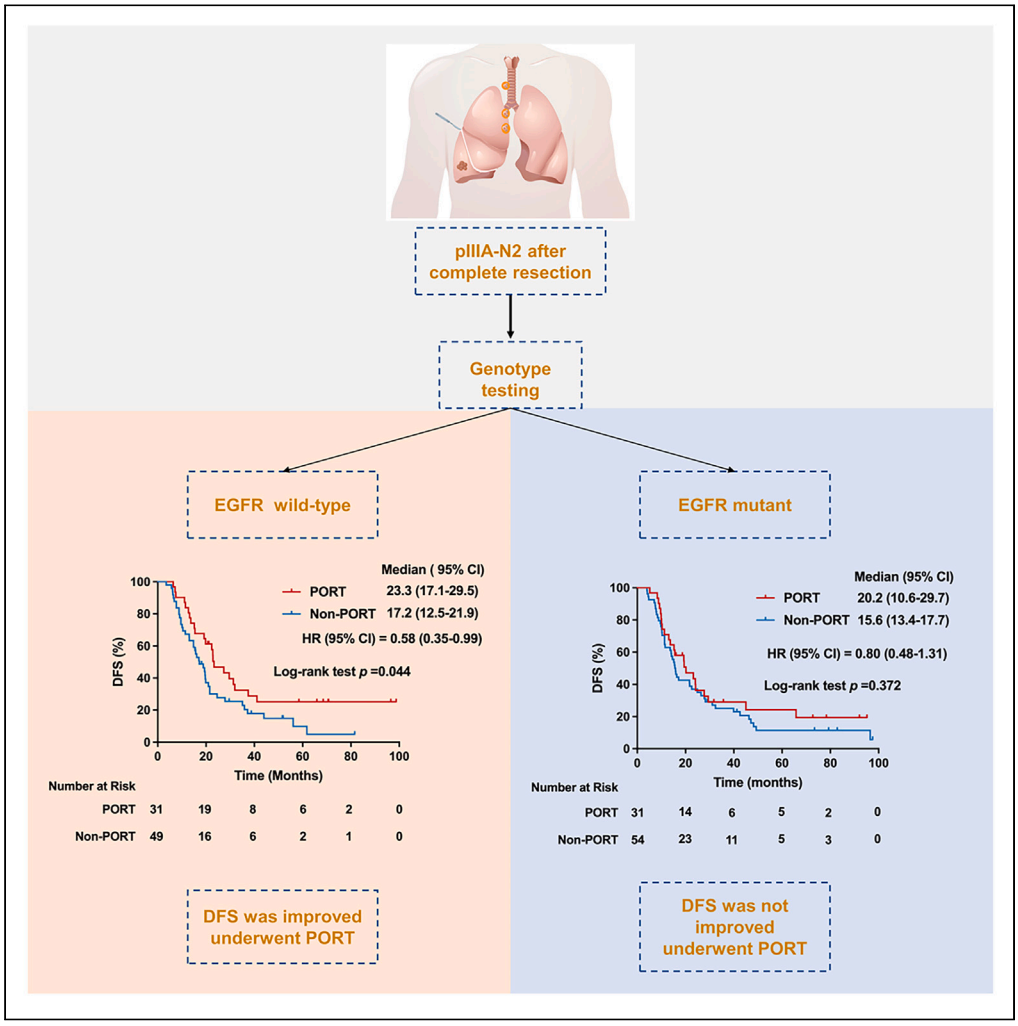

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Highlights

DFS was improved in both overall and EGFR wild-type patients receiving PORT

PORT was not correlated with improved survival outcomes in EGFR mutation patients

EGFR wild-type may a biomarker to identify the cohort that benefits from PORT

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The efficacy of postoperative radiotherapy in resected pIIIA-N2 EGFR mutant and wild-type lung adenocarcinoma

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SUMMARY

The resected pIIIA-N2 non-small-cell lung cancer (NSCLC) patients who could benefit from postoperative radiotherapy (PORT) are not well-defined. The study explored the role of PORT on EGFR mutant and wild-type NSCLC patients. We retrospectively searched for resected pIIIA-N2 lung adenocarcinoma patients who underwent EGFR mutation testing. 80 patients with EGFR wild-type and 85 patients with EGFR mutation were included. 62 patients received PORT. In overall population, the median disease-free survival (DFS) was improved in PORT arm compared to non-PORT arm (22.9 vs. 16.1 months; $p = 0.036$), along with higher 2-year locoregional recurrence-free survival (LRFS) rate (88.3% vs. 69.3%; $p = 0.004$). In EGFR wild-type patients, PORT was associated with a longer median DFS (23.3 vs. 17.2 months; $p = 0.044$), and a higher 2-year LRFS rate (86.8% vs. 61.9%; $p = 0.012$). In EGFR mutant patients, PORT was not significantly correlated with improved survival outcomes. EGFR wild-type may a biomarker to identify the cohort that benefits from PORT.

INTRODUCTION

The role of postoperative radiotherapy (PORT) was controversial for pathologic stage IIIA non-small-cell lung cancer with mediastinal lymph node metastasis (pIIIA-N2 NSCLC). Numerous studies, including analyses of databases such as the National Cancer Database and Surveillance, Epidemiology, and End Results (SEER) database, as well as retrospective studies, have consistently demonstrated the benefits of PORT in reducing risks of locoregional recurrence and improving survival outcomes for patients with pIIIA-N2 NSCLC.[1–5] Phase III randomized clinical trials including the Lung-ART study and the PORT-C study have demonstrated that PORT exhibited a non-statistically significant improvement in disease-free survival (DFS) in intent-to-treat population (ITT).[6,7] The PORT-C study has suggested that PORT can still have a favorable effect on local control and significantly improve DFS and locoregional recurrence-free survival (LRFS) rate in the per-protocol populations.[6] Therefore, it is essential to identify the biomarkers to determine the cohorts that could benefit most from PORT.

From the past year, some retrospective studies have identified clinicopathological factors that were associated with the efficacy of PORT in patients with pIIIA-N2 NSCLC. Patients with higher age, males, with higher T stage, ≥6 positive lymph nodes metastases, N2 multi-station metastasis, and positive lymph nodes ratio ≤20%, tended to benefit from PORT adjuvant therapy.[8–12] Epidermal growth factor receptor (EGFR) mutation status is a critical determinant in treatment decision-making in the era of precision medicine. Furthermore, studies have shown that differential responses to low dose and low fraction-sized irradiation occurred in both EGFR wild-type and EGFR mutant NSCLC cell lines.[13] However, there is currently no clinical evidence demonstrating whether the EGFR mutation status of lung cancer is associated with the efficacy of PORT.

Adjuvant EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib and osimertinib showed improved survival outcomes for resected EGFR mutant NSCLC patients.[14,15] However, the patients who underwent PORT were excluded from these studies. As of yet, there is no clinical data showed IIIA-pN2 EGFR mutant patients should withdraw PORT. For patients with resected EGFR wild-type NSCLC, adjuvant programmed

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cell death ligand 1 (PD-L1) inhibitors showed DFS benefit in PD-L1 positive NSCLC patients.[16] However, adjuvant atezolizumab has a duration of one year and may potentially increase the incidence of adverse events. The role of PORT needs to be explored in light of advancements in perioperative management. Therefore, we conducted a clinical study to elucidate the efficacy of PORT in pIIIA-N2 lung adenocarcinoma with identified EGFR mutation status.

RESULTS

Baseline characteristics

A total of 165 patients were included in this study, and the clinicopathological characteristics of patients were summarized in detail in Table1. In overall population, there were 62 patients in the PORT arm and 103 patients in the non-PORT arm. The median interval time between surgery and initiation of adjuvant chemotherapy was 32 days (range 7–82). In the PORT arm, 98.4% of patients received intensity-modulated radiation therapy (IMRT). The median planning target volume dosage was 50 Gy (range 47.3–62.0) in 23–30 daily fractions. There were 80 and 85 patients were patients with EGFR wild-type and EGFR mutation. In the EGFR wild-type patients, there were 31 patients in the PORT arm and 49 patients in the non-PORT arm. In the EGFR mutant patients, there were 31 patients in the PORT arm and 54 patients in the non-PORT arm. In overall population, a higher trend of N2 multi-station metastasis was showed in the PORT arm. The baseline characteristics were well-balanced in the PORT and non-PORT arm in EGFR wild-type and EGFR mutant group (Table 2).

Patterns of the first failure

There were 133 DFS of first failure events, which were composed of 45 patients and 88 patients in the PORT and the non-PORT arm relapses (72.6% vs. 85.4%, $p = 0.043$). 5 and 22 patients experienced locoregional recurrence (including synchronous locoregional recurrence and distant metastasis), and the occurrence rate in the PORT was lower than non-PORT arm (8.1% vs. 21.4%, $p = 0.025$, Figure 1A). 43 and 74 patients experienced distant metastasis for the PORT and non-PORT arm (69.4% vs. 71.8%, $p = 0.733$).

In EGFR wild-type patients, 22 patients in the PORT and 41 patients in the non-PORT arm relapsed (71.0% vs. 83.7%, $p = 0.176$, Figure 1B). The occurrence rates of locoregional recurrence (13.0% vs. 18.4%, $p = 0.519$) and distant metastasis (64.5% vs. 75.5%, $p = 0.290$) were not statistically different in PORT and non-PORT arm. In EGFR mutant patients, 23 patients in the PORT and 47 patients in the non-PORT arm relapsed (74.2% vs. 87.0%, $p = 0.135$, Figure 1C). There was a significant reduction in locoregional recurrence associated with PORT (3.2% vs. 24.0%, $p = 0.013$), but not in the distant metastasis (74.2% vs. 68.5%, $p = 0.580$).

Survival outcomes in overall population

The median follow-up time was 79.3 months (95% CI 73.0–85.6). The median DFS for patients in the PORT arm and non-PORT arm was 22.9 months (95% CI 18.6–27.1) and 16.1 months (95% CI 13.1–19.2). The PORT was significantly associated with better DFS than non-PORT arm (hazard ratio [HR] 0.68; 95% CI 0.47–0.98; $p = 0.036$, Figure 2A). Besides, the 2-year LRFS rate was higher in the PORT arm (88.3% vs. 69.3%; $p = 0.004$, Figure 2B) compared with the non-PORT arm. The median distant metastasis-free survival (DMFS) were 23.3 months (95% CI 19.3–27.3) and 19.4 months (95% CI 15.1–23.7), respectively (HR 0.78, 95% CI 0.54–1.13, $p = 0.189$; Figure 2C). A total of 103 events of death were reported. The median overall survival (OS) was 46.5 months (95% CI 31.2–61.7) in the PORT arm and 59.3 months (95% CI 46.2–72.4) in the non-PORT arm (HR 1.04, 95% CI 0.70–1.55, $p = 0.843$; Figure 2D).

Survival outcomes in EGFR wild-type and EGFR mutant groups

31 (38.8%) and 49 (61.3%) patients with EGFR wild-type were in the PORT and non-PORT arms. Compared with non-PORT arm, PORT was associated with improved the median DFS (23.3 vs. 17.2 months; HR 0.58, 95% CI 0.35–0.99; $p = 0.044$, Figure 3A) and 2-year LRFS rate (86.8% vs. 61.9%; $p = 0.012$, Figure 3B). The median DMFS was prolonged in the PORT arm (27.4 vs. 17.2 months; HR 0.56, 95% CI 0.33–0.95, $p = 0.030$, Figure 3C). The median OS for patients was 42.0 months and 40.0 months respectively (HR 0.77, 95% CI 0.44–1.33; $p = 0.350$, Figure 3D).

31 (36.5%) and 54 (63.5%) patients with EGFR mutation were in the PORT arm and non-PORT arm, respectively. The median DFS for patients was 20.2 months and 15.6 months (HR 0.80, 95% CI 0.48–1.31; $p = 0.372$, Figure 4A) in PORT and non-PORT arm. The 2-year LRFS rate had no significantly difference (90.0% vs. 75.7%; $p = 0.083$, Figure 4B) in two arms. The median DMFS were 20.2 months and 21.7 months (HR 1.09; 95% CI 0.65–1.81, $p = 0.746$, Figure 4C) and median OS was 62.4 months and 70.7 months with no significant difference (HR 1.24, 95% CI 0.70–2.20; $p = 0.469$, Figure 4D).

Survival outcomes with different N2 station metastasis

In overall population, PORT demonstrated a favorable effect on DFS (27.7 vs. 21.5 months; HR 0.48, 95% CI 0.27–0.88, $p = 0.018$, Figure S1A) in patients with N2 single-station metastasis but not in those with N2 multi-station metastasis (19.8 vs. 13.0 months; HR 0.73, 95% CI 0.46–1.17, $p = 0.188$, Figure S1B). However, PORT was associated with an improved 2-year LRFS rate (88.7% vs. 60.7%, $p = 0.003$) in patients with N2 multi-station metastasis. PORT showed no correlation with OS in both N2 single-station and multi-station metastasis subgroups.

In EGFR wild-type patients, PORT showed favorable effect on DFS (not reached vs. 21.0 months; HR = 0.34, 95% CI 0.13–0.93, $p = 0.036$, Figure S1C) in patients with N2 single-station metastasis but not in those with N2 multi-station metastasis (22.8 vs. 13.1 months; HR 0.66, 95% CI 0.35–1.28, $p = 0.220$, Figure S1D). PORT significantly improved and 2-year LRFS rate (90.0% vs. 52.2%, $p = 0.004$) in patients N2 multi-station metastasis. In EGFR mutant patients, there is no difference of DFS in N2 single-station and multi-station metastasis (Figures S1E and S1F).

Table 1. Clinicopathological characteristics in PORT and non-PORT arm in overall population

Characteristics	Total (*n* = 165)	PORT (*n* = 62)	Non-PORT (*n* = 103)	*p* value[a]
Sex				0.522
Male	104 (63.0)	41 (66.1)	63 (61.2)	
Female	61 (37.0)	21 (33.9)	40 (38.8)	
Age (years)				0.699
≤60	125 (75.8)	48 (77.4)	77 (74.8)	
>60	40 (24.2)	14 (22.6)	26 (25.2)	
Smoking status				0.981
Never	96 (58.2)	36 (58.1)	60 (58.3)	
Former or current	69 (41.8)	26 (41.9)	43 (41.7)	
VATS				0.885
No	49 (29.7)	18 (29.0)	31 (30.1)	
Yes	116 (70.3)	44 (71.0)	72 (69.9)	
Type of surgery				0.257
Lobectomy	158 (95.8)	61 (98.4)	97 (94.2)	
Pneumonectomy	7 (4.2)	1 (1.6)	6 (5.8)	
Location				0.135
Left lung	57 (34.5)	17 (27.4)	40 (38.8)	
Right lung	108 (65.5)	45 (72.6)	63 (61.2)	
Tumor size (cm)				0.533
≤3	88 (53.3)	35 (56.5)	53 (51.5)	
>3	77 (46.7)	27 (43.5)	50 (48.5)	
Differentiation				0.505
~Moderately	88 (53.3)	31 (50.0)	57 (55.3)	
~Poorly	77 (46.7)	31 (50.0)	46 (44.7)	
Visceral pleura				0.945
Negative	107 (64.8)	40 (64.5)	67 (65.0)	
Positive	58 (35.2)	22 (35.5)	36 (35.0)	
N1 node involvement				0.709
No	62 (37.6)	18 (29.0)	44 (42.7)	
Yes	103 (62.4)	44 (71.0)	59 (57.3)	
N2 multi-station metastasis				0.095
No	83 (50.3)	26 (41.9)	57 (55.3)	
Yes	82 (49.7)	36 (58.1)	46 (44.7)	
N2 positive node ratio				0.280
≤0.4	107 (64.8)	37 (59.7)	70 (68.0)	
>0.4	58 (35.2)	25 (40.3)	33 (32.0)	
EGFR status				0.763
Wild-type	80 (48.5)	31 (50.0)	49 (47.6)	
Mutation	85 (51.5)	31 (50.0)	54 (52.4)	
Positive N2 nodes, median (range)	2 (1–15)	3 (1–10)	2 (1–15)	

[a]*p* values were calculated using two-sided $\chi 2$ test and Fisher's exact test (for low-sample dichotomous data)

Cox multivariate analysis of predictors for survival

The factors of PORT, tumor size, N1 node involvement, N2 different station metastasis, and N2 positive node ratio, surgery type, and EGFR mutation status were included in the Cox multivariate analysis of DFS. The result demonstrated that PORT (HR 0.63, 95% CI 0.44–0.91, p = 0.013) and Use of VATS (HR 0.63, 95% CI 0.44–0.90, p = 0.010) were prognostic factors for improved DFS, and N2 positive node ratio >0.4 was associated with a worse DFS (HR 1.63, 95% CI 1.10–2.44, p = 0.016, Figure S2). Age, tumor size, EGFR mutation status, N2 different station

Table 2. Clinicopathological characteristics in PORT and non-PORT arm in EGFR wild-type and EGFR mutant patients

	EGFR wild-type			EGFR mutation		
Characteristics	PORT (*n*=31)	Non-PORT (*n*=49)	*p* value	PORT (*n*=31)	Non-PORT (*n*=54)	*p* value[a]
Sex			0.731			0.296
Male	23 (74.2)	38 (77.6)		18 (58.1)	25 (46.3)	
Female	8 (25.8)	11 (22.4)		13 (41.9)	29 (53.7)	
Age (years)			0.817			0.481
≤60	24 (77.4)	39 (79.6)		24 (77.4)	38 (70.4)	
>60	7 (22.6)	10 (20.4)		7 (22.6)	16 (29.6)	
Smoking status			0.506			0.532
Never	15 (48.4)	20 (40.8)		21 (67.7)	40 (74.1)	
Former or current	16 (51.6)	29 (59.2)		10 (32.3)	14 (25.9)	
VATS			0.516			0.380
No	11 (35.5)	14 (28.6)		7 (22.6)	17 (31.5)	
Yes	20 (64.5)	35 (71.4)		24 (77.4)	37 (68.5)	
Type of surgery			0.279			1.000
Lobectomy	31 (100)	46 (93.9)		30 (96.8)	51 (94.4)	
Pneumonectomy	0 (0)	3 (6.1)		1 (3.2)	3 (5.6)	
Location			0.213			0.419
Left lung	6 (19.4)	16 (32.7)		11 (35.5)	24 (44.4)	
Right lung	25 (80.6)	33 (67.3)		20 (64.5)	30 (55.6)	
Tumor size (cm)			0.982			0.378
≤3	17 (54.8)	27 (55.1)		18 (58.1)	26 (48.1)	
>3	14 (45.2)	22 (44.9)		13 (41.9)	28 (51.9)	
Differentiation			0.405			0.978
~Moderately	11 (35.5)	22 (44.9)		20 (64.5)	35 (64.8)	
~Poorly	20 (64.5)	27 (55.1)		11 (35.5)	19 (35.2)	
Visceral pleura			0.285			0.249
Negative	22 (71.0)	29 (59.2)		18 (58.1)	38 (70.4)	
Positive	9 (29.0)	20 (40.8)		13 (41.9)	16 (29.6)	
N1 node involvement			0.210			0.168
No	12 (38.7)	26 (53.1)		6 (19.4)	18 (33.3)	
Yes	19 (61.3)	23 (46.9)		25 (80.6)	36 (66.7)	
N2 multi-station metastasis			0.124			0.442
No	11 (35.5)	26 (53.1)		15 (48.4)	31 (57.4)	
Yes	20 (64.5)	23 (46.9)		16 (51.6)	23 (42.6)	
N2 positive node ratio			0.101			0.987
≤0.4	18 (58.1)	37 (75.5)		19 (61.3)	33 (61.1)	
>0.4	13 (41.9)	12 (24.5)		12 (38.7)	21 (38.9)	
Positive N2 nodes, Median (range)	3 (1–9)	2 (1–15)		3 (1–10)	2 (1–15)	

[a]*p* values were calculated using two-sided $\chi 2$ test and Fisher's exact test (for low-sample dichotomous data)

metastasis, and N2 nodes positive ratio, N1 metastasis and PORT were included the in Cox multivariate analysis of OS, which showed that EGFR mutant status was an independent prognostic factor for improved OS (HR 0.52, 95% CI 0.35–0.77, $p = 0.001$), and N2 multi-station metastasis showed inferior OS (HR 2.22, 95% CI 1.48–3.33, $p < 0.001$). In EGFR wild-type patients, PORT was the only factor associated with improved DFS (HR 0.56, 95% CI 0.33–0.95; $p = 0.033$, Figure 5A). N2 multi-station metastasis is the inferior factor of OS (HR 2.54, 95% CI 1.39–4.60, $p = 0.003$). In EGFR mutant patients, N2 positive node ratio >0.4 (HR 2.79, 95% CI 1.67–4.70, $p < 0.001$) and N1 modes involvement (HR 1.96, 95% CI 1.06–3.60, $p = 0.031$) were associated with the worse DFS (Figure 5B). N2 positive node ratio >0.4 is the factor of inferior OS (HR 2.00, 95% CI 1.10–3.60; $p = 0.016$).

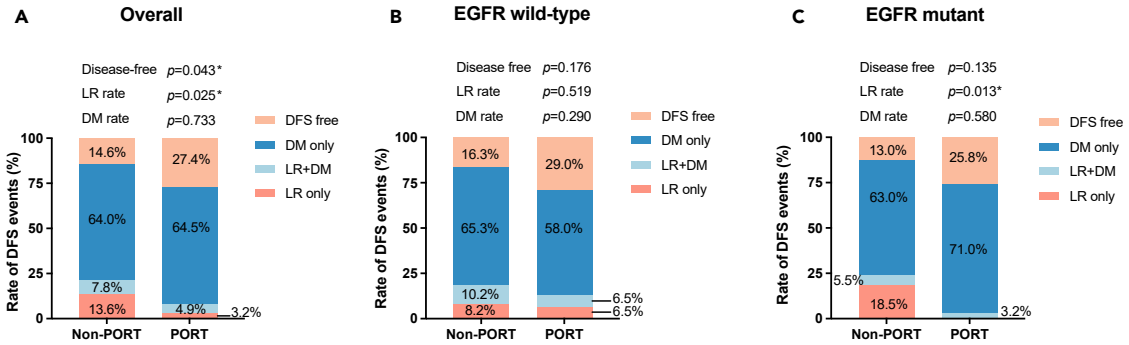

Figure 1. Patterns of the first failure

(A) The overall population.

(B) EGFR wild-type patients.

(C) EGFR mutant patients.

p values were calculated using two-sided $\chi 2$ test. Abbreviatios : LR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival.

Subgroup analyses of survival in the overall population

In general, PORT was associated with better DFS trends in the subgroup analysis. As compared with the comparator adjuvant chemotherapy, the DFS benefit with PORT was showed in the subgroup of males, aged beyond 60, EGFR wild-type, location of right lung lobe, tumor size

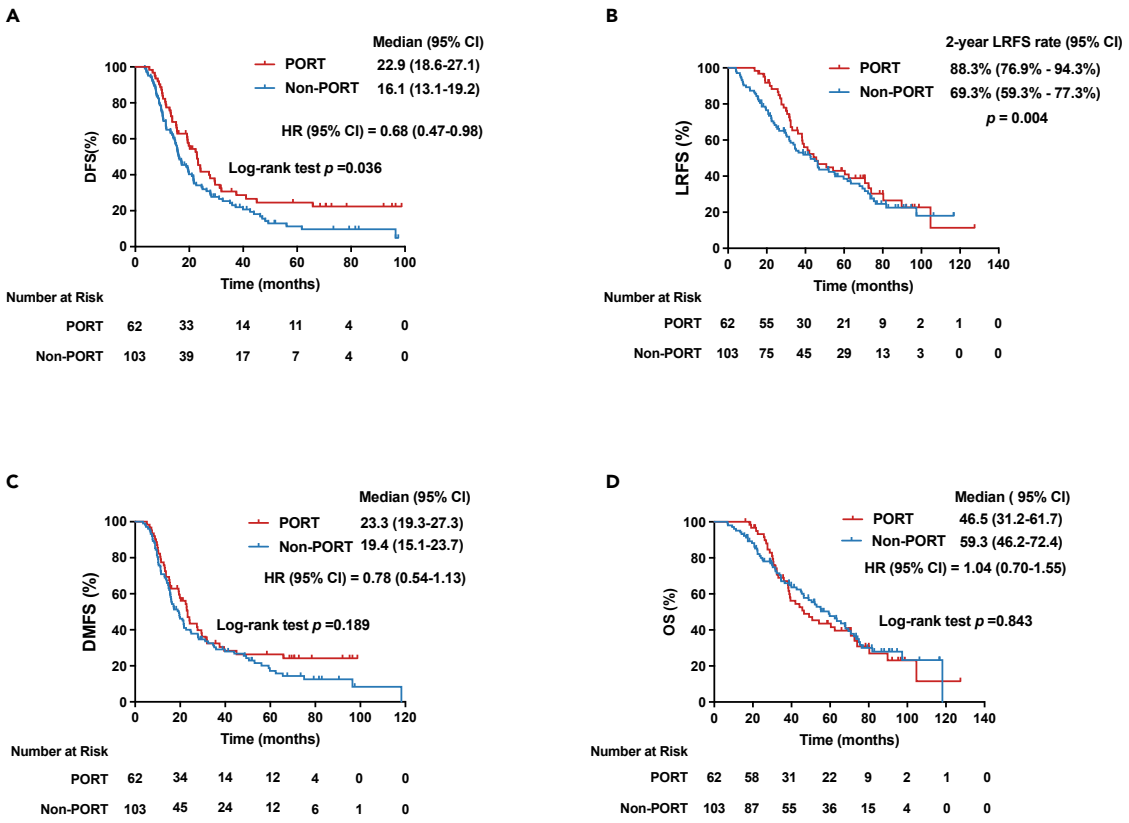

Figure 2. Kaplan-Meier survival estimates for survival outcomes in overall population

(A) Kaplan-Meier estimates of the duration of DFS.

(B) Kaplan-Meier estimates the duration of LRFS.

(C) Kaplan-Meier estimates the duration of DMFS.

(D) Kaplan-Meier estimates the duration of OS.

(A, C, and D) *p* values were caculated using the two-sided log-rank test. (B) *p* value of comparison of 2-year LRFS was based on Z-Test.

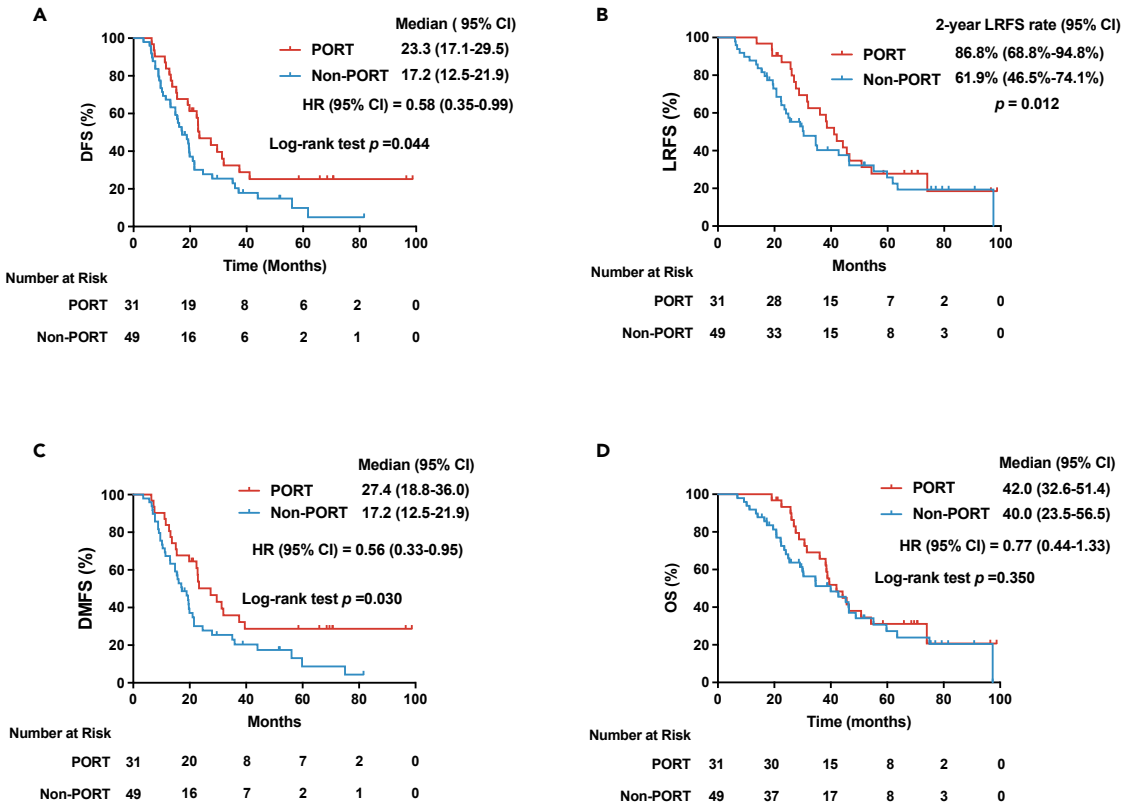

Figure 3. Kaplan-Meier survival estimates for survival outcomes in EGFR wild-type groups

(A) Kaplan-Meier estimates of the duration of DFS.

(B) Kaplan-Meier estimates the duration of LRFS.

(C) Kaplan-Meier estimates the duration of DMFS.

(D) Kaplan-Meier estimates the duration of OS.

(A, C, and D) *p* values were caculated using the two-sided log-rank test. (B) *p* value of comparison of 2-year LRFS was based on Z-Test.

>3 cm, with N1 nodes involved, N2 single-station metastasis, and N2 positive node ratio ≤0.4 (Figure 6). No significant benefits of OS in each subgroup (Table S1).

DISCUSSION

The LungART study and PORT-C study both indicated that PORT decreased the locoregional relapse but was not statistically associated with improved DFS in the ITT population with IIIA-pN2.[6,7] In the LungART study, PORT could decrease the mediastinal relapse rate but bring higher thoracic adverse events in grades 3–5 (AEs),[7] which revealed thatthree-dimensional conformal radiotherapy (3DCRT) was not the appropriate technique. In the PORT-C study, 89.3% of patients received IMRT with no occurrence of grades 4 or 5 AEs. PORT showed improved LRFS benefit in the ITT population and improved DFS and LRFS in the per-protocol population and as-treated population.[6] More, the DFS significantly differed after stratification according to the number of detected N2 nodes and positive N2 nodes. Hence, there is a need to explore the most beneficial cohort for PORT. The genetic status should be considered; however, the efficacy of PORT on patients with different genetic statuses was not revealed in the LungART study and PORT-C study.

In the era of precision medicine, adjuvant targeted therapy had adorable efficacy in EGFR mutant NSCLC.[14,15,17] The prognostic significance of EGFR mutation status in patients who underwent PORT was unclear.[18,19] In our study, the results revealed that PORT was not associated with better survival outcomes in pIIIA-N2 NSCLC with EGFR mutation, which suggested that targeted therapy may be a more suitable adjuvant treatment option. For EGFR wild-type patients, the options for adjuvant therapies are limited. Our study found that PORT was associated with improved DFS, including local control and distant metastasis. Therefore, EGFR wild-type patients may benefit from PORT and could consider it as adjuvant therapy. Additionally, the prevalence rate of EGFR mutation was 51.5% (85/165), which can be attributed to the study population consisting of patients with lung adenocarcinoma, a type of lung cancer for which genotype testing is routinely recommended. The prevalence rate of EGFR mutation aligns with reported literature, which suggests mutations occur in 40–60% of East Asian lung adenocarcinoma cases.[20]

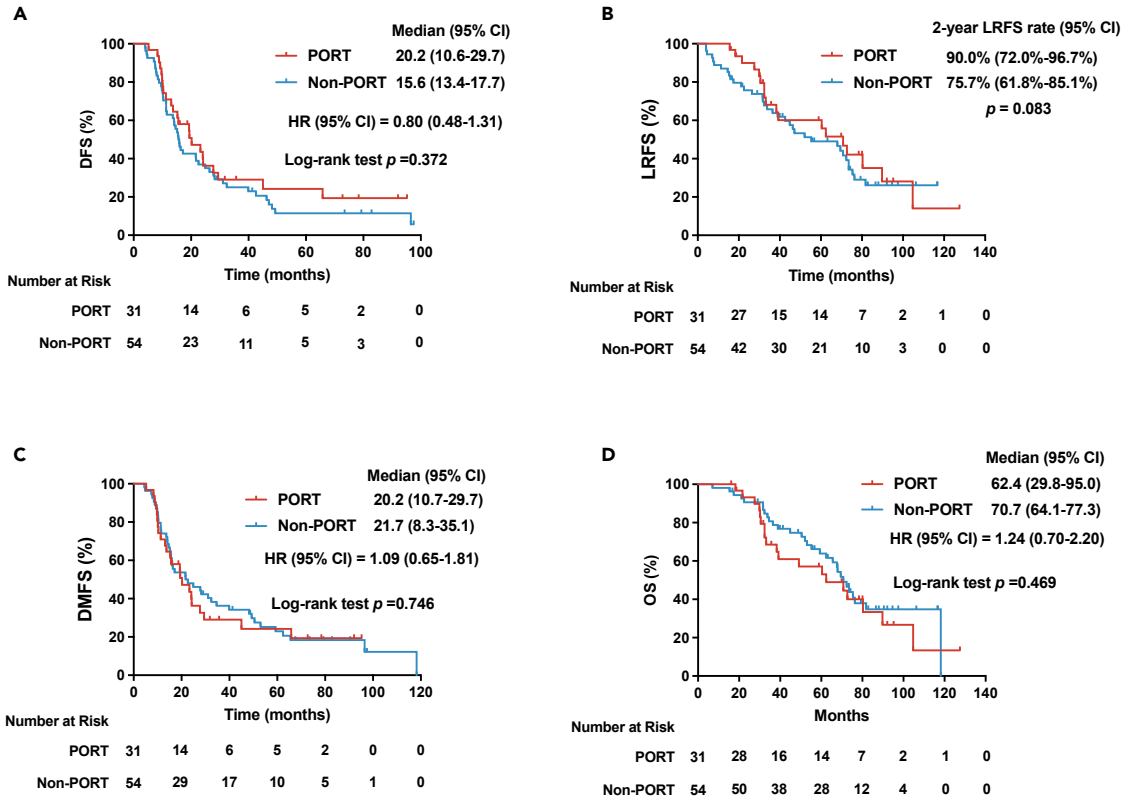

Figure 4. Kaplan-Meier survival estimates for survival outcomes in EGFR mutant groups

(A) Kaplan-Meier estimates of the duration of DFS.

(B) Kaplan-Meier estimates the duration of LRFS.

(C) Kaplan-Meier estimates the duration of DMFS.

(D) Kaplan-Meier estimates the duration of OS.

(A, C, and D) *p* values were caculated using the two-sided log-rank test. (B) *p* value of comparison of 2-year LRFS was based on Z-Test.

In the past decade, there have been revolutionary advancements in postoperative therapy. The exploration of optimal options has led to the investigation of immune checkpoint inhibitors (ICIs) as both neoadjuvant and adjuvant therapies.[16,21] Neoadjuvant nivolumab plus chemotherapy brought a satisfactory survival with a huge percentage of pathological complete response in IB to IIIA NSCLC.[21] However,

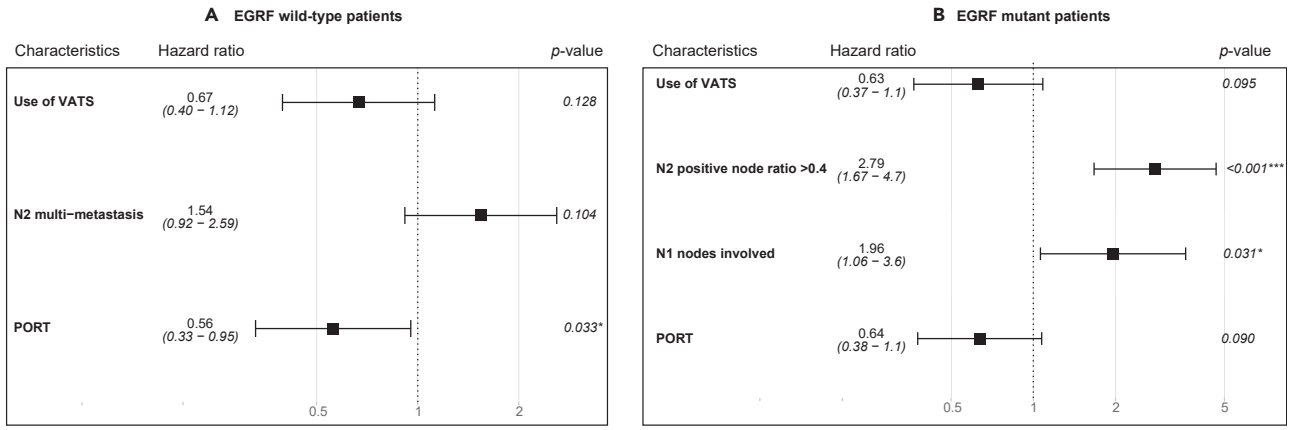

Figure 5. Multi-Cox regression of disease-free survival in EGFR wild-type and EGFR mutant patients

(A) The forest plot of multi-Cox regression of DFS among EGFR wild-type patients.

(B) The forest plot of multi-Cox regression of DFS among EGFR mutation patients.

p values were caculated using two-sided multi-Cox regression.

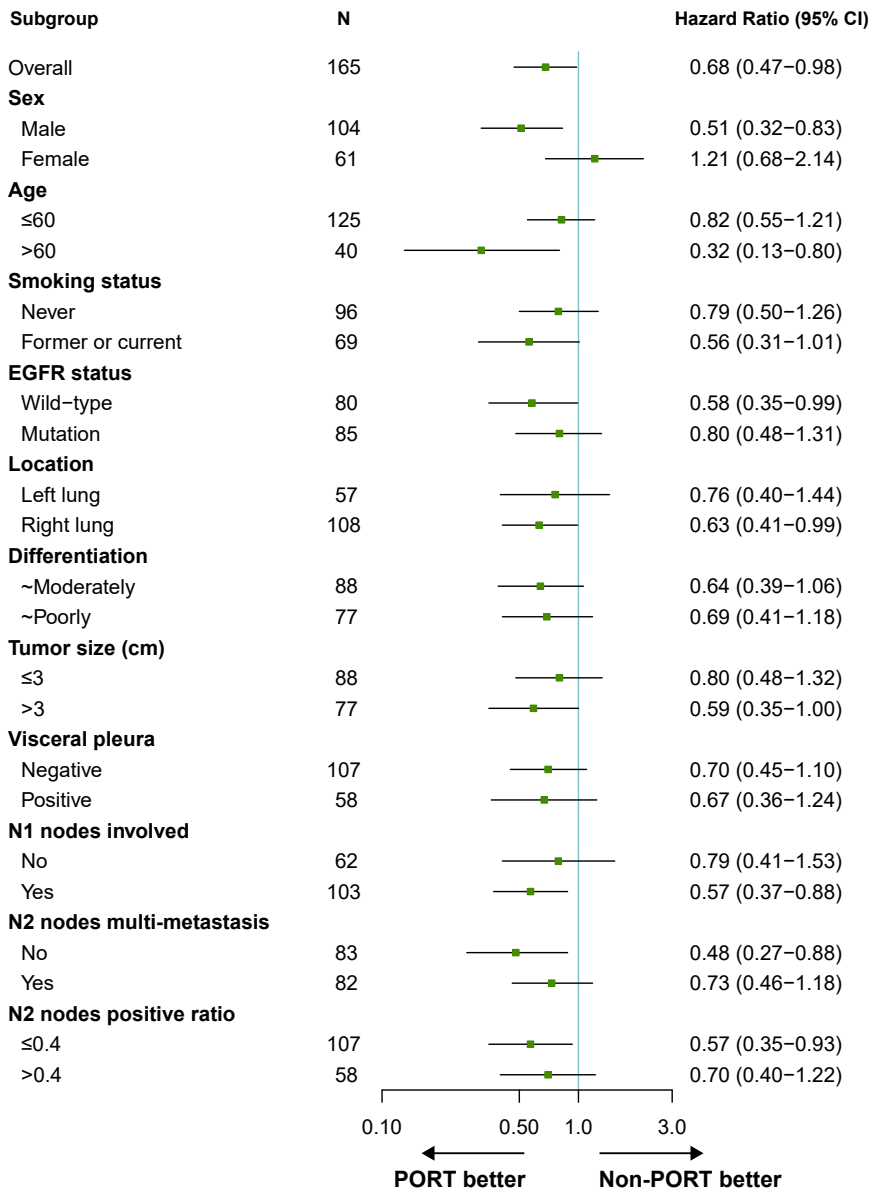

Figure 6. Subgroup analysis of disease-free survival in PORT and non-PORT arms

The subgroup analysis was performed with the use of a Cox proportional-hazards model. The outer dashed lines indicate the 95% confidence interval for the overall hazard ratio. A hazard ratio of less than 1 implies a lower risk of disease recurrence with PORT than with non-PORT.

the locoregional recurrence was the major reason of recurrences in the neoadjuvant nivolumab plus chemotherapy group (28/43). Besides, half of patients in the chemotherapy group suffered from locoregional recurrence in Checkmate 816 study.[22] The value of PORT in patients who underwent neoadjuvant immunotherapy should be further investigated. Impower 010 study showed a DFS benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients whose tumor PD-L1 $\geq$1 with resected stage II–IIIA NSCLC.[16] The Keynote 091 reported that survival benefits were presented from adjuvant pembrolizumab in all patients of IB-IIIA patients after completed resection.[23] Radiotherapy may have a synergistic effect combined with ICIs therapy by overcoming tumor immune tolerance and evasion mechanisms.[24,25] Considering immunotherapy following adjuvant PORT using the IMRT technique, along with monitoring for adverse events, may be a viable therapy approach to consider in future study designs. The presence of minimal residual disease (MRD) after surgical resection could be detected by circulating tumor DNA and predicting the relapse.[26] The utilization of MRD detection after complete resection to decide whether PORT should be conducted may be the exploratory direction. The optimal adjuvant therapy based on molecular subtyping were summarized in Figure 7

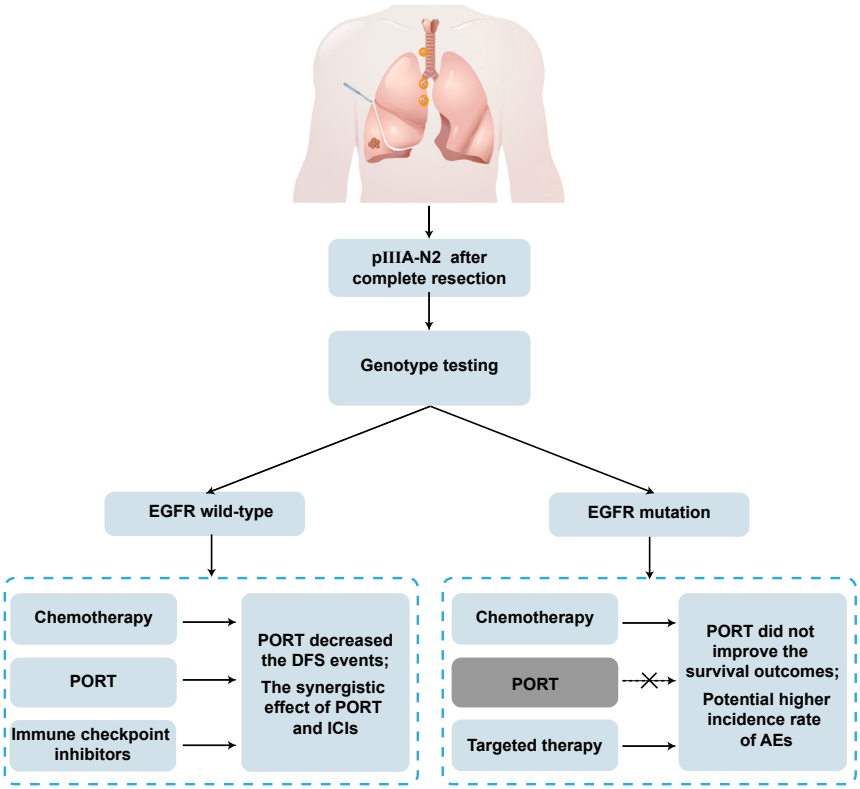

Figure 7. The choices of pIIIA-N2 patients after complete resection with differential EGFR mutation status (by Figdraw)

It was controversial which type of N2-station involvement will benefit from PORT most. There is a suggestion that PORT might be particularly beneficial for patients with N2 single-station metastasis, especially when concurrent with N1 node involvements.[27,28] By contrast, some studies supported PORT could improve prognosis in N2 multi-station group.[10,29] In this study, PORT exhibited favorable effects on DFS in EGFR wild-type patients with N2 single-station metastasis. Additionally, EGFR wild-type patients with N2 multi-station metastases also experienced benefits in terms of local control.

In summary, we firstly reported the efficacy of PORT in pIIIA-N2 patients with different EGFR mutation status. The optimal adjuvant therapy based on molecular subtyping was summarized. The PORT had a favorable effect on DFS including locoregional recurrence and distant metastasis in EGFR wild-type lung adenocarcinoma patients but not in those with EGFR mutant patients. EGFR wild-type patients of lung adenocarcinoma with pIIIA-N2 could be considered to receive PORT as adjuvant therapy.

Limitations of the study

The study has some limitations. It is a retrospective study with not so large population, which may be affected by potential confounding factors. Besides, the study population comprised solely Chinese individuals with lung adenocarcinoma, necessitating further investigations in larger, diverse cohorts encompassing different races and pathologies.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110219.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
GraphPad Prism 7	GraphPad Software	https://www.graphpad.com/scientific-software/prism/
R 4.1.2	R Software	https://cran.r-project.org/bin/windows/base/old/4.1.2/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to lead contact, Fang Wu (wufang4461@csu.edu.cn)

Materials availability

This study did not use any reagents.

Data and code availability

- De-identified patient standardized data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design and participants

The study was conducted at the Second Xiangya University of Central South University, Xiangya Hospital of Central South University, and Hunan Cancer hospital from January 2012 to December 2020. Lung adenocarcinoma Chinese patients who received complete resection with stage pIIIA-N2 would be included (by AJCC TNM 7th edition before 2018, the 8th edition after 2018). All patients received platinum-based adjuvant chemotherapy for 3–4 cycles within 3 months after surgery. Afterwards, according to whether treated with PORT, patients were divided into two groups. Simultaneous and sequential PORT were eligible. EGFR mutation status was identified by real-time fluorescence quantitative polymerase chain reaction or next-generation sequencing. The inclusion criteria are mainly as follows: adults aged ranges 18 years–75 years, histologically proven lung adenocarcinoma NSCLC of stage pT1-3N2M0, identified EGFR mutation status (EGFR mutant or wild-type), adjuvant therapy of chemotherapy. Patients excluded who received system therapy with diseases that recurred or metastasized under adjuvant therapy, uncompleted radiotherapy plan, ALK and ROS1 fusion, and neoadjuvant therapy and/or adjuvant targeted therapy (Figure S3). It's worth noting that the patients with EGFR mutation can receive EGFR-TKIs therapy upon disease relapse.

The information of age, biological sex, smoking history, type of surgery, tumor location, tumor size, tumor pathology, lymph nodes pathology, radiotherapy technique, radiotherapy dose, radiotherapy dosage, EGFR mutation status, medical examinations, and detailed management process were obtained from the electronic medical record systems. The date of surgical resection, PORT, last follow-up, disease relapse, and death was collected for analysis. Record the DFS events and survival outcome with the last follow-up time of March 1, 2022. The study was approved by the ethics committee of the Second Xiangya Hospital of Central South University (No. 2020009).

METHOD DETAILS

Interventions for surgery

Complete resection was defined as lobectomy surgery or pneumonectomy with free resection margins proved microscopically systematic nodal dissection or lobe-specific systematic nodal dissection, and no extracapsular nodal extension of the tumor.[30] Systematic nodal dissection requires all of the following[31]: N1 nodes (stations 10), superior mediastinal nodes (station 4), subcarinal nodes (station 7), and inferior mediastinal nodes (stations 8 or 9 if accessible) for right lung cancer. When lesions locating in the left lobe, N1 nodes (stations 10), superior mediastinal nodes (station 4 if accessible), aortic nodes (stations 5–6), subcarinal nodes (station 7) should be cleared. Open operation and video-assisted thoracoscopic surgery (VATS) were allowed for surgery.

Postoperative chemotherapy

All patients were treated with 3–4 cycles of adjuvant chemotherapy within 3 months after surgery. The standard adjuvant chemotherapy is platinum-based dual-drug chemotherapy, every 3 weeks for each cycle.[32]

PORT

All patients in the PORT group were treated using the radiotherapy techniques of the three-dimensional conformal radiotherapy (3DCRT) technique or intensity-modulated radiation therapy (IMRT). Clinical target volume (CTV) includes the ipsilateral mediastinal nodes, subcarinal nodes, and ipsilateral hilum, intrapulmonary node drainage area of the lesion operation side. The planning target volume (PTV) was defined as the CTV plus the 0.5 cm margins. The dose constraints for the organ at risk (OAR) were as follows: a maximum dose to the spinal cord of less than 40 Gy; volume (V) percentage of organs receiving a specific gray dose: to the esophagus, V50 less than 50%; to the heart, V30 less than 40%, V40 less than 30%; to the whole lung, V20 less than 20% after pulmonary lobectomy and V20 less than 10% after pneumonectomy.

Assessments and definitions

Follow-up assessments were conducted for evaluating image logical examination (computed tomography, magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography-computed tomography. DFS was defined as the duration between the date after surgery to the date of any recurrence or death firstly (determined by image logical examination, pathological disease on biopsy, or both). Locoregional recurrence-free survival (LRFS) was defined as the duration between the date of surgery to the date of locoregional recurrence or death. Distant metastasis-free survival (DMFS) was defined as the duration between the date of surgery to the date of any distant metastasis or death. Overall survival (OS) was defined as the duration between the date after surgery to the date of death from any cause.

QUANTIFICATION AND STATISTICAL ANALYSIS

Proportion comparisons analyses utilized the $\chi 2$ test and Fisher's exact test (for low-sample dichotomous data). $\chi 2$ test was conducted to evaluate the difference in DFS events occurrences between the PORT and non-PORT arms. The outcome survival analyses were estimated using the Kaplan-Meier method and compared with log-rank tests. The comparison of 2-year survival rates was based on Z-Test. The subgroup analysis was based on the Cox regression models. A multivariable model was developed using Cox regression by selecting variable which was related to survival outcomes in clinic. Differences were assumed to be significant when the two-sided p-value < 0.05. All statistical analyses were conducted using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA), GraphPad (Prism 7, Boston, USA) and R version 4.1.2.