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Postoperative radiotherapy improves disease-free survival of EGFR wild-type pN2 non-squamous-cell non-small-cell lung cancer (Nsq-NSCLC) patients after complete resection: a propensity score matching analysis

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Abstract

Background The ADAURA study indicated that adjuvant TKI therapy improves survival in postoperative patients with EGFR-mutated (EGFRm) non-small-cell lung cancer (NSCLC), especially in stage III disease. However, the effect of PORT for stage III (N2) NSCLC with different EGFR statuses remains unclear, which we aimed to investigate in the present study.

Methods Between 2006 and 2019, consecutive patients with pN2 non-squamous cell NSCLC (Nsq-NSCLC) after complete resection and adjuvant chemotherapy or EGFR tyrosine kinase inhibitor (TKI) who had detection of EGFR status were retrospectively analyzed. PORT was administered using IMRT at 2 Gy per fraction with a total dose of 50 Gy over 5 weeks. Patients were categorized into 4 groups according to EGFR status and treatment: EGFR wild-type (EGFRwt) PORT group, EGFRwt non-PORT group, EGFRm PORT group, and EGFRm non-PORT group. Propensity score matching (PSM) was used to compensate for differences in baseline characteristics. The Kaplan-Meier method and log-rank test were used to evaluate disease-free survival (DFS), locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS).

Results A total of 566 patients were enrolled: 90 in the EGFRwt PORT group, 154 in the EGFRwt non-PORT group, 111 in the EGFRm PORT group, and 211 in the EGFRm non-PORT group. After PSM, the median DFS in the EGFRwt PORT group versus the EGFRwt non-PORT group were 33.9 versus 17.2 months (HR 0.62, 95%CI 0.417–0.920, $P=0.017$). In EGFRwt groups, PORT also improved LRFS (HR 0.58, 95%CI 0.34–0.99, $P=0.042$) and DMFS (HR 0.649, 95%CI 0.43–0.98,

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$P = 0.038$). In EGFRm groups, PORT only improved LRFS (HR 0.50, 95%CI 0.30–0.85, $P = 0.009$), with no significant difference in DFS or DMFS between the PORT and non-PORT groups.

Conclusion For patients with completely resected pN2 Nsq-NSCLC receiving adjuvant chemotherapy, PORT may improve DFS in EGFRwt patients but not in EGFRm patients. Randomized clinical trials are needed for validation.

Keywords Postoperative radiotherapy, Non-squamous-cell non-small-cell lung cancer, EGFR, Survival

Background

The role of postoperative radiotherapy (PORT) for pN2 non-small cell lung cancer (NSCLC) has been controversial for a long time [1–3]. Recently, two phase III randomized control trial, PORT-C and Lung-ART [4, 5], showed consistent results that PORT showed a tendency to improve disease-free survival (DFS) but failed to achieve statistical significance. Therefore, identifying proper subgroups who can benefit from PORT is possible and crucial.

EGFR status has been established as an independent prognostic factor [6], and its assessment is recommended in patients with non-squamous cell NSCLC (Nsq-NSCLC). It is related to the biological behavior of NSCLC after resection, with EGFR wild-type (EGFRwt) patients having a higher risk of locoregional recurrence, while EGFR-mutated (EGFRm) patients have a higher risk of distant metastasis [7]. Therefore, the effect of adjuvant therapy may vary based on EGFR status. Adjuvant tyrosine kinase inhibitors (TKI) have shown significant improvement in DFS in completely resected stage IB to IIIA EGFRm NSCLC [8], making it a recommended treatment. However, the value of PORT in EGFRm patients has not been fully investigated and the relationship between EGFR status and radiosensitivity remains controversial [9]. Moreover, for EGFRwt patients, the value of adjuvant immunotherapy remains uncertain based on recent studies [10, 11]; although perioperative immunotherapy has shown improved event-free survival, the recurrence rate remains high [12]. For pN2 NSCLC receiving surgery, median DFS is merely around 20 months, with 46% of patients suffering from mediastinal relapse [4, 5], so exploring better adjuvant treatment modalities is necessary. Currently, the benefit of PORT based on different EGFR status in pN2 Nsq-NSCLC patients remains unclear.

In this retrospective study, the efficacy was compared between PORT and non-PORT in EGFRwt and EGFRm patients, respectively, to support the individualized treatment for completely resected pN2 Nsq-NSCLC receiving adjuvant chemotherapy or TKI.

Methods

Patients

Between May 2006 and June 2019, consecutive patients with pN2 NSCLC in our institution were analyzed. The stage was based on the 7th edition of the American Joint Committee on Cancer and International Union Against Cancer TNM stage classification for lung cancer. The inclusion criteria were: (1) histologically confirmed pN2 Nsq-NSCLC, (2) underwent complete resection (R0), (3) had detection of EGFR status, (4) received adjuvant chemotherapy or adjuvant EGFR TKI, (5) aged 18 or older, (6) Karnofsky performance status > 70. Patients with incomplete medical records of inclusion criteria were excluded. PORT was administered using intensity-modulated radiation therapy (IMRT) at 2 Gy per fraction up to 50 Gy over 5 weeks after adjuvant chemotherapy of a platinum-based doublet regimen. The clinical target volume (CTV) included the ipsilateral hilum, subcarinal region, ipsilateral mediastinum, and the stump of the central lesions. The institutional review boards approved this retrospective study and the requirement for informed consent was waived.

Patients were categorized into 4 groups according to EGFR status and whether PORT was administered: EGFRwt PORT group, EGFRwt non-PORT group, EGFRm PORT group, and EGFRm non-PORT group.

Outcomes

DFS was defined as the time interval from the date of surgery to recurrence or death, whichever occurred first. Locoregional relapse-free survival (LRFS) was measured from the date of surgery to locoregional recurrence or death, whichever occurred first. Distant metastasis-free survival (DMFS) was measured from the date of surgery to distant metastasis or death, whichever occurred first. All time-to-event data were censored at the last follow-up if the event-of-interest didn't occur. Overall survival (OS) was not tested because the data were immature. Outcomes were compared between the EGFRwt PORT group and the EGFRwt non-PORT group; and between the EGFRm PORT group and the EGFRm non-PORT group. Furthermore, an exploratory subgroup analysis was performed to compare outcomes in EGFRm patients receiving adjuvant TKI and the EGFRm PORT group.

Statistical analysis

The DFS, LRFS, and DMFS were estimated using the Kaplan-Meier method, and the statistical difference was determined using the log-rank test. The Hazard Ratios (HRs) were calculated with their 95% confidence

intervals (CIs) by COX regression. Propensity score matching (PSM) was performed using the nearest neighbor method with a caliper of 0.1. Characteristics were evaluated between treatment groups using Fisher's exact test for categorical variables and the t-test or Wilcoxon ranked sum test for continuous variables. A two-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 26.0 and R 4.1.2 software.

Results

Patients' characteristics

From 950 patients screened, 566 patients were enrolled, including 90 in the EGFRwt PORT group, 154 in the EGFRwt non-PORT group, 111 in the EGFRm PORT group, and 211 in the EGFRm non-PORT group (Fig. 1). The median age was 57 years (interquartile range (IQR): 50–64) and 298 (52.7%) were female. The median follow-up time was 35.6 months (IQR: 25.8–56.6). The baseline characteristics of the EGFRwt groups are shown in Table 1. All characteristics were balanced between the EGFRwt PORT group and the EGFRwt non-PORT group except for age ($P = 0.016$), clinical N stage ($P = 0.032$), and the number of positive lymph nodes ($P = 0.034$). The baseline characteristics of the EGFRm groups are shown in Table 2. All characteristics were balanced between the EGFRm PORT group and the EGFRm non-PORT group except for the number of positive lymph nodes ($P = 0.046$) and the use of adjuvant EGFR TKI ($P = 0.003$).

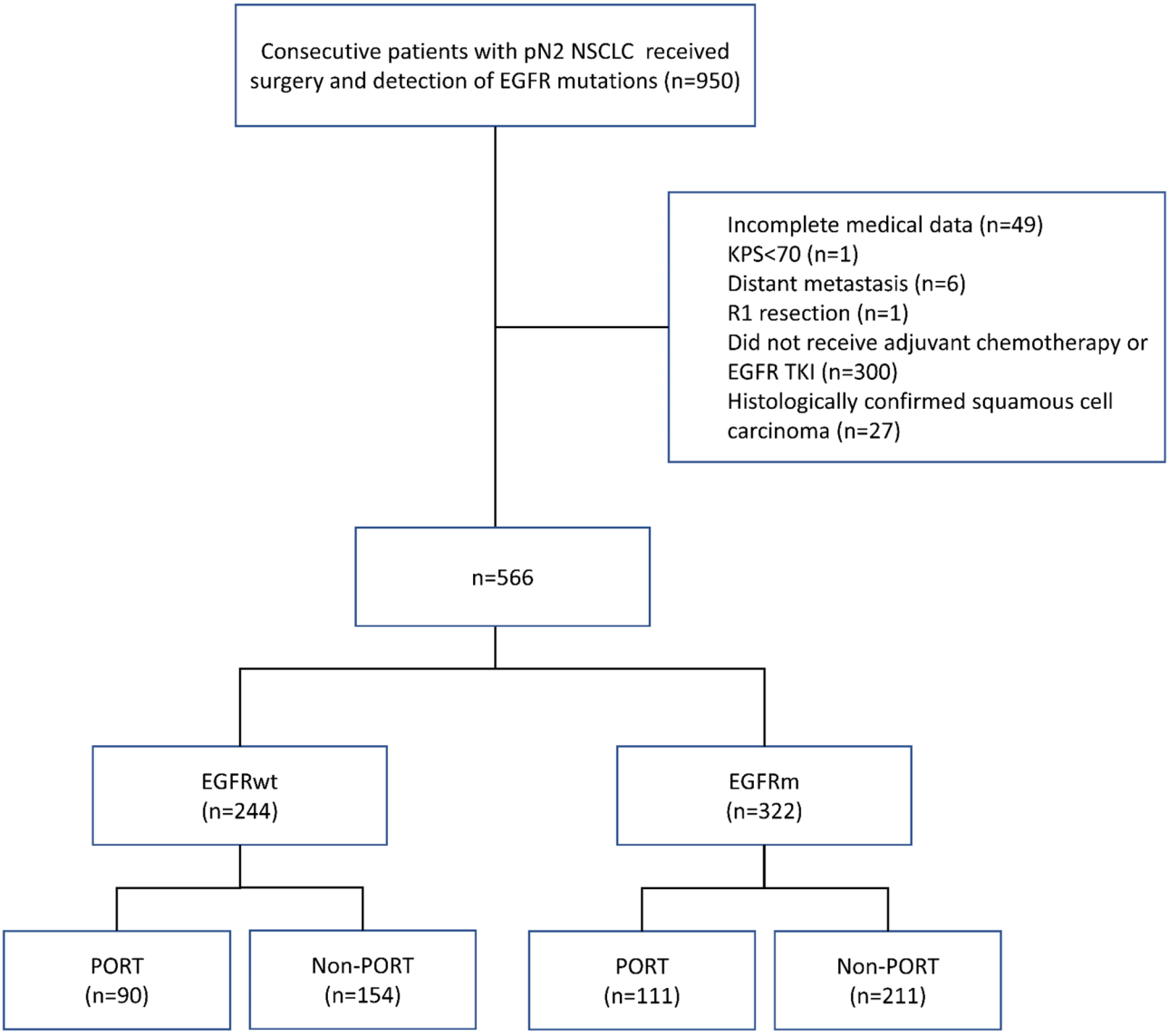

Fig. 1 Selection process of patients. pN, pathological N stage; NSCLC, non-small-cell lung cancer; KPS, Karnofsky performance status; TKI, tyrosine kinase inhibitors; EGFRwt, EGFR wild-type; EGFRm, EGFR-mutated; PORT, postoperative radiotherapy

Table 1 EGFRwt patients' characteristics

	Non-PORT (*n* = 154)	PORT (*n* = 90)	*P* value
Age	60 (50, 65)	57 (48, 62)	0.016
Sex			> 0.999
Female	58 (37.7)	34 (37.8)	
Male	96 (62.3)	56 (62.2)	
Smoking history	76 (49.4)	39 (43.3)	0.425
KPS			0.744
> 80	124 (80.5)	71 (78.9)	
≤ 80	30 (19.5)	19 (21.1)	
Tumor location			0.227
Left lung	70 (45.5)	33 (36.7)	
Right lung	84 (54.5)	57 (63,3)	
cT			0.708
1	50 (32.9)	30 (33.3)	
2	87 (57.2)	52 (57.8)	
3	14 (9.2)	6 (6.7)	
4	1 (0.7)	2 (2.2)	
Missing data	2	0	
cN			0.032
0	80 (52.3)	42(46.7)	
1	21 (13.7)	6 (6.7)	
2	48 (31.4)	42 (46.7)	
3	4 (2.6)	0 (0.0)	
Missing data	1	0	
Cycles of chemotherapy			
< 4	21 (15.3)	5 (6.2)	0.114
4	106 (77.4)	71 (87.7)	
> 4	10 (7.3)	5 (6.2)	
Missing data	17	9	
pT			0.366
1	29 (18.8)	23 (25.6)	
2	92 (59.7)	44 (48.9)	
3	30 (19.5)	20 (22.2)	
4	3 (1.9)	3 (3.3)	
Positive lymph nodes			0.034
≤ 5	92 (59.7)	41 (45.6)	
> 5	62 (40.3)	49 (54.4)	
Histology	61 (21.3)	22 (21.2)	0.303
Adenocarcinoma	141 (91.6)	86 (95.6)	
Others [a]	13 (8.4)	4 (4.4)	
Surgery type			0.799
Open	76 (49.4)	43 (47.8)	
Thoracoscopic	78 (50.6)	47 (52.2)	

Data are median (IQR) or n (%) unless otherwise specified. a, including adenosquamous carcinoma, large cell carcinoma and other rare histology types. IQR, interquartile range; KPS, Karnofsky performance status; cT, clinical T stage; cN, clinical N stage; pT, pathological T stage

Table 2 EGFRm patients' characteristics

	Non-PORT (*n* = 211)	PORT (*n* = 111)	*P* value
Age	56 (51, 63)	56 (49, 62)	0.251
Sex			0.089
Female	142 (67.3)	64 (57.7)	
Male	69 (32.7)	47 (42.3)	
Smoking history	57 (27.0)	30 (27.0)	> 0.999
KPS			0.683
> 80	162 (76.8)	83 (74.8)	
≤ 80	49 (23.2)	28 (25.2)	
Tumor location			0.727
Left lung	109 (51.7)	55 (49.5)	
Right lung	102 (48.3)	56 (50.5)	
cT			0.706
1	83 (39.9)	38 (35.2)	
2	115 (55.3)	65 (60.2)	
3	10 (4.8)	5 (4.6)	
Missing data	3	3	
cN			0.778
0	117 (56.3)	56 (50.9)	
1	28 (13.5)	16 (14.5)	
2	56 (26.9)	35 (31.8)	
3	7 (3.4)	3 (2.7)	
Missing data	3	1	
pT			0.876
1	36 (19.1)	21 (19.6)	
2	126 (67.0)	68 (63.6)	
3	22 (11.7)	15 (14)	
4	4 (2.1)	3 (2.8)	
Missing data	0	2	
Positive lymph nodes			0.046
≤ 5	109 (51.7)	44 (39.6)	
> 5	102 (48.3)	67 (60.4)	
Cycles of chemotherapy			
< 4	31 (16.8)	7 (7.1)	0.114
4	140 (75.7)	86 (86.9)	
> 4	14 (7.6)	6 (6.1)	
Missing data/ no chemotherapy	26	12	
Histology	61 (21.3)	22 (21.2)	0.173
Adenocarcinoma	202 (95.7)	110 (99.1)	
Others [a]	9 (4.3)	1 (0.9)	
EGFR mutations			0.550
19 del	101 (47.9)	58 (52.3)	
21 L858R	87 (41.2)	39 (35.1)	
Others [b]	23 (10.9)	14 (12.6)	
Surgery type			0.288
Open	98(46.4)	44 (39.6)	
Thoracoscopic	113 (53.6)	67 (60.4)	
Adjuvant TKI	14 (6.6)	0 (0.0)	0.003

Data are median (IQR) or n (%) unless otherwise specified. a, including adenosquamous carcinoma, large cell carcinoma and other rare histology types. b, including 18 exon, 20 exon and mixed mutations. IQR, interquartile range; KPS, Karnofsky performance status; cT, clinical T stage; cN, clinical N stage; pT, pathological T stage; TKI, tyrosine kinase inhibitors

PORT versus non-PORT in EGFRwt patients

The median DFS in the PORT and non-PORT groups were 33.9 months (95%CI 23.1-not reached (NR) months) and 19.3 months (95%CI 16.4–31.5 months), respectively. The PORT group had marginally better DFS than the non-PORT group (HR 0.717, 95%CI 0.51–1.01,

$P = 0.056$) (Fig. 2A). The median LRFS was not reached in both PORT and non-PORT groups (HR 0.77, 95%CI 0.46–1.13, $P = 0.154$) (Fig. 2B). DMFS was also not significantly different (HR 0.75, 95% CI 0.52–1.07, $P = 0.107$), with a median of 37.7 months (95%CI 26.1-NR months) in the PORT group and 23.7 months (95%CI 18.1–41.6 months) in the non-PORT group.

PORT versus non-PORT in EGFRm patients

The median DFS in the PORT and non-PORT groups were 20.2 months (95%CI 16.3–29.7 months) and 25.7 months (95%CI 20.3–35.5 months), respectively, with no significant difference (HR 1.12, 95%CI 0.84–1.50, $P = 0.424$) (Fig. 2A). The median LRFS was not reached in the PORT group and was 102 months (95%CI 66.6-NR months) in the non-PORT group (HR 0.74, 95%CI 0.47–1.17, $P = 0.192$) (Fig. 2B). Likewise, the DMFS was not significantly different between the two groups (HR 1.14, 95%CI 0.85–1.53, $P = 0.397$) (Fig. 2C).

PSM analysis

For EGFRwt patients, PSM analysis was performed with the following covariate variables: age, sex, number of positive lymph nodes, and clinical N stage. Patients' characteristics were balanced after PSM with 84 patients in each group (Table 3). The median DFS in the PORT and non-PORT groups were 33.9 months (95%CI 23.1-NR months) and 17.2 months (95%CI 13.3–39.6 months), respectively. The PORT group had significantly better DFS than the non-PORT group (HR 0.62, 95%CI 0.42–0.92, $P = 0.017$) (Fig. 3A). The median LRFS was not reached in the PORT group and was 72.9 months (95%CI 49.9-NR months) in the non-PORT group (HR 0.58, 95%CI 0.34–0.99, $P = 0.042$) (Fig. 3B). The median DMFS was 49.4 months (95%CI 26.1-NR months) in the PORT group, compared with 20.8 months (95%CI 16.1–44.4 months) in the non-PORT group (HR 0.649, 95%CI 0.43–0.98, $P = 0.038$) (Fig. 3C).

For EGFRm patients, PSM analysis was performed with the following covariate variables: age, sex, number of positive lymph nodes, cycles of adjuvant chemotherapy, and use of TKI. Patients' characteristics were balanced after PSM with 95 patients in each group (Table 4). The median DFS was 19.9 months (95%CI 16.1–32.8 months) in the PORT group, compared with 19.0 months (95%CI 12.4–30.9 months) in the non-PORT group (HR 0.91, 95%CI 0.64–1.29, $P = 0.600$) (Fig. 3A). The median LRFS was significantly longer in the PORT group (not reached) than in the non-PORT group (66.4 months, 95%CI 39.9-NR months) (HR 0.50, 95%CI 0.30–0.85, $P = 0.009$) (Fig. 3B). The DMFS remained non-significantly different between the two groups after PSM (HR 0.92, 95%CI 0.64–1.32, $P = 0.655$) (Fig. 3C).

Adjuvant TKI and PORT in EGFRm patients

A total of 322 EGFRm patients were divided into 197 with adjuvant chemotherapy only, 14 with adjuvant TKI, and 111 with PORT. Baseline characteristics are shown in eTable 1. There was no significant difference in DFS ($P = 0.710$), LRFS ($P = 0.424$), and DMFS ($P = 0.623$) (eFigure 1). The PSM analysis was performed on patients who received adjuvant chemotherapy at a ratio of 1:4 based on the following covariate variables: age, sex, number of positive lymph nodes, and pT. Sixty-three patients (28 in the adjuvant chemotherapy group, 28 in the PORT group, and 7 in the TKI group) were matched with balanced characteristics (eTable 2). Kaplan-Meier curves showed no significant difference in DFS ($P = 0.441$), LRFS ($P = 0.218$), and DMFS ($P = 0.449$), but the TKI group tended to have better DFS and DMFS (eFigure 2).

Discussion

Our findings suggest that PORT may prolong DFS in EGFRwt patients with Nsq-NSCLC who have received adjuvant chemotherapy. However, in EGFRm patients, PORT failed to show improvement in efficacy. This study is notable for evaluating the efficacy of PORT in completely resected pN2 NSCLC, considering distinct EGFR statuses.

Although recent studies, such as the LungART and PORT-C trials, have shown that PORT does not improve survival in patients with stage IIIA-pN2 NSCLC, they did not conduct subgroup analyses based on EGFR status [4, 5]. Our study, however, observed significantly better DFS, locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) in EGFRwt patients who received PORT compared to those who did not. In contrast, for EGFRm patients, PORT only significantly improved LRFS compared to the non-PORT group. These findings suggest that PORT has a comprehensively favorable efficacy in EGFRwt patients, while its advantage is limited in EGFRm patients.

In a previous retrospective study involving EGFRwt NSCLC patients, PORT ($n = 41$) was found to significantly reduce recurrence compared to surgery alone ($n = 42$), suggesting the potential of PORT to improve disease control in EGFRwt patients [13]. However, this study had a small sample size, and the control group did not receive adjuvant chemotherapy. Our study expands on these findings, demonstrating the clinical value of PORT in EGFRwt patients under modern standard treatment protocols.

Currently, there is limited research focusing on EGFRwt pN2 Nsq-NSCLC, although a few investigations have been conducted in the immunotherapy era, and their results remain controversial. In the IMpower010 trial, the median DFS in the adjuvant atezolizumab group was significantly longer than that in the supportive care

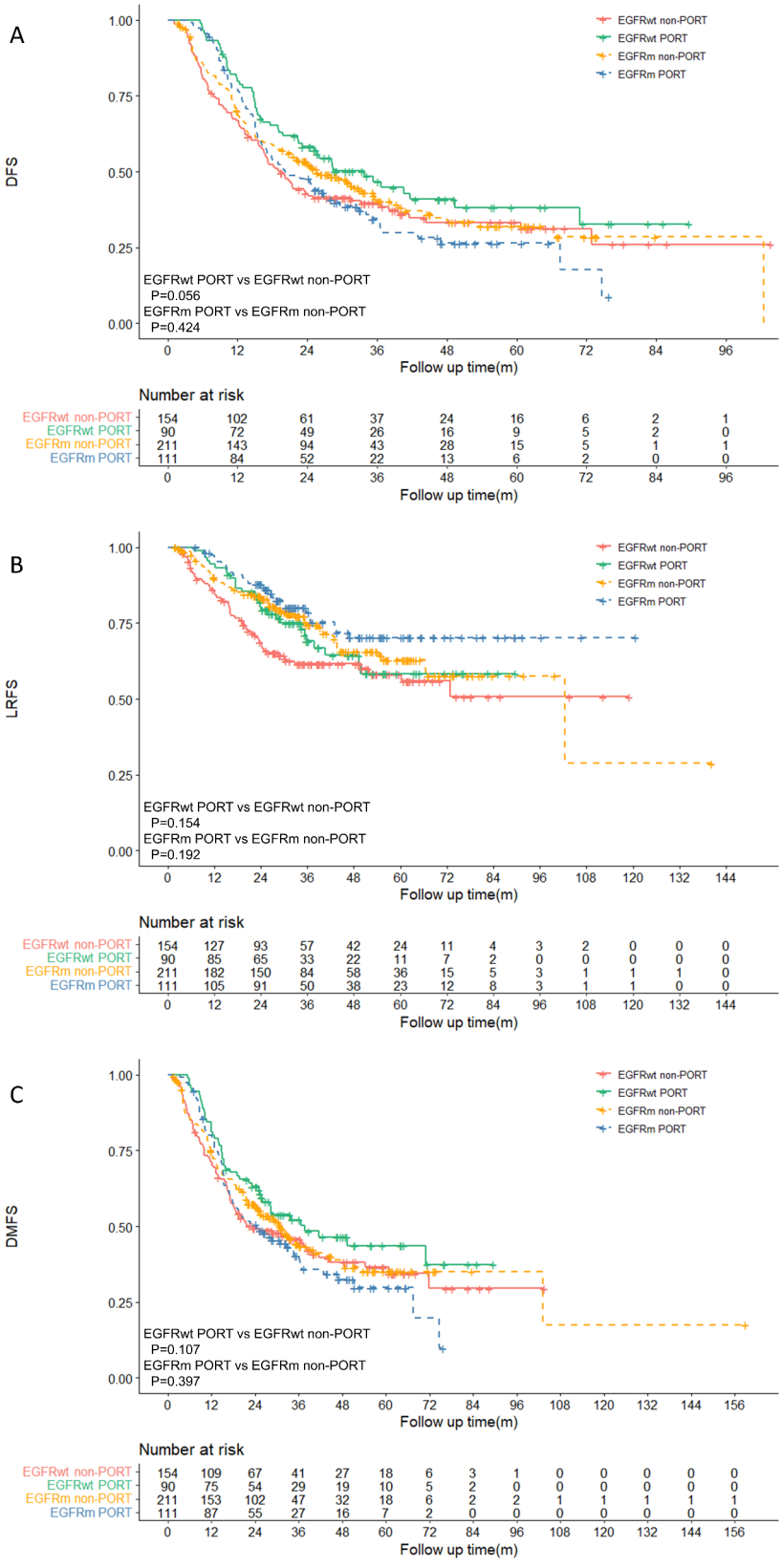

Fig. 2 Kaplan-Meier Curves before propensity score matching. PORT, postoperative radiotherapy; DFS, disease-free survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival

Table 3 EGFRwt patients' characteristics after PSM

	Non-PORT (*n* = 84)	PORT (*n* = 84)	*P* value
Age	57 (48, 62)	57 (48, 62)	0.979
Sex			0.875
Female	35 (41.7)	49 (58.3)	
Male	49 (58.3)	35 (41.7)	
Smoking history	37 (44.0)	35 (41.7)	0.876
KPS			0.851
> 80	65 (77.4)	67 (79.8)	
≤ 80	19 (22.6)	17 (20.2)	
Tumor location			0.159
Left lung	40 (47.6)	30 (35.7)	
Right lung	44 (52.4)	54 (64,3)	
cT			0.715
1	27 (32.5)	28 (33.3)	
2	45 (54.2)	48 (57.1)	
3	10 (12.0)	6 (7.1)	
4	1 (1.2)	2 (2.4)	
Mssing data	1	0	
cN			0.324
0	37 (44.0)	40 (47.6)	
1	12 (14.3)	6 (7.1)	
2	34 (40.5)	38 (45.2)	
3	1 (1.2)	0 (0.0)	
Cycles of chemotherapy			
< 4	12 (16.4)	5 (6.7)	0.191
4	56 (76.7)	65 (86.7)	
> 4	5 (6.8)	5 (6.7)	
Missing data	11	9	
pT			0.178
1	14 (16.7)	21 (25.0)	
2	46 (54.8)	40 (47.6)	
3	24 (28.6)	20 (23.8)	
4	0 (0.0)	3 (1.8)	
Positive lymph nodes			> 0.999
≤ 5	40 (47.6)	39 (46.4)	
> 5	44 (52.4)	45 (53.6)	
Histology	61 (21.3)	22 (21.2)	0.535
Adenocarcinoma	77 (91.7)	86 (95.6)	
Others [a]	7 (8.3)	4 (4.4)	
Surgery type			0.322
Open	44 (52.4)	43 (47.8)	
Thoracoscopic	40 (47.6)	47 (52.2)	

Data are median (IQR) or n (%) unless otherwise specified. a, including adenosquamous carcinoma, large cell carcinoma and other rare histology types. IQR, interquartile range; KPS, Karnofsky performance status; cT, clinical T stage; cN, clinical N stage; pT, pathological T stage

group (HR 0.66, 95% CI 0.50–0.88, $p = 0.0039$) for postoperative stage II–IIIA NSCLC with PD-L1 ≥ 1% [10]. Subgroup analysis based on EGFR status showed a borderline improvement of DFS in the EGFRwt population (HR 0.67, 95% CI 0.45–1.00). By contrast, the phase III BR.31 trial, which included stage IB–IIIA NSCLC without EGFR mutations, revealed no significant improvement in DFS with adjuvant immunotherapy (HR 0.89, 95% CI 0.75–1.07) [11]. In the phase III Neotorch trial, perioperative toripalimab significantly improved event-free survival compared to placebo in EGFRwt stage II–III NSCLC (HR 0.40, 95% CI 0.28–0.57), yet the 2-year DFS was only 56.8% following perioperative immunotherapy, indicating considerable room for further efficacy gains [12]. Our study shows that adding PORT after adjuvant chemotherapy increased the median DFS from 17.2 months to 33.9 months and reduced the risk of recurrence or death by 38%, with corresponding improvements in LRFS and DMFS. These findings suggest that PORT may be a valuable treatment approach to explore for EGFRwt pN2 Nsq-NSCLC, even in the immunotherapy era.

In a retrospective study including 91 EGFRm NSCLC patients who underwent curative resection and received adjuvant chemotherapy without TKI, the PORT group ($n = 28$) did not show a significant improvement in DFS compared to the non-PORT group ($n = 63$) ($P = 0.067$) [14], which is consistent with the findings of our study. One possible reason is that postoperative recurrence in EGFRm NSCLC patients is mainly distant metastasis, while the locoregional recurrence is significantly fewer than in EGFRwt patients, thereby diminishing the potential benefit of PORT [7, 15]. For EGFRm NSCLC patients, in the ADAURA trial, the TKI group demonstrated a significant improvement in DFS compared to the placebo group (HR 0.17, 99.06% CI 0.11–0.26), as well as the OS (HR 0.49, 95.03%CI 0.34–0.70) [16, 17]. Additionally, the randomized phase III ADJUVANT trial showed that gefitinib extended DFS [18], and the randomized phase II EVANS study reported prolonged DFS and OS in patients receiving adjuvant erlotinib [19, 20]. Our study specifically explored the efficacy of adjuvant TKI therapy in EGFRm patients and showed a trend towards improved DFS and DMFS with adjuvant TKI therapy compared to PORT or adjuvant chemotherapy alone. Given the limited benefit observed with PORT in EGFRm patients and the significant benefit demonstrated by previous studies with TKIs, it suggests that routine PORT may not be recommended after adjuvant TKI therapy in EGFRm patients. It is important to note that the ADAURA trial showed that even after adjuvant osimertinib, 8% of patients experienced locoregional recurrence [16]. With regular follow-up examinations, PORT can be considered as salvage therapy for patients with locoregional recurrence. Besides, previous small-scale study showed that PORT improved DFS in N2-positive patients with lymphovascular invasion and/or CK5/6 expression ($P = 0.041$), suggesting the possibility of identifying the subgroup of EGFRm patients who may benefit from PORT [14].

Our study has several limitations. First, it is a retrospective single-center study, and the sample size was reduced after propensity score matching. Second, most

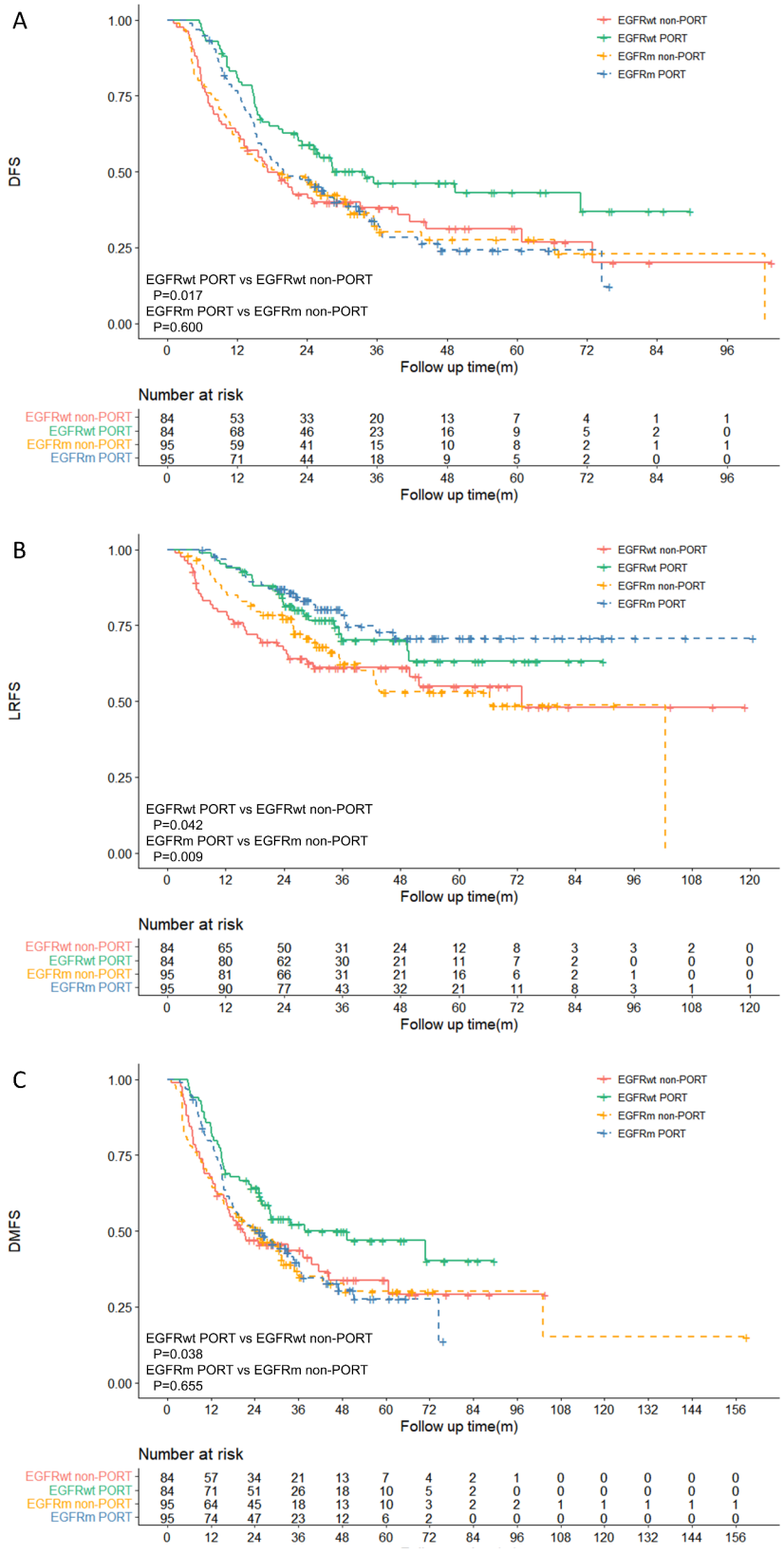

Fig. 3 Kaplan-Meier Curves after propensity score matching. PORT, postoperative radiotherapy; DFS, disease-free survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival

Table 4 EGFRm patients' characteristics after PSM

	Non-PORT (*n* = 95)	PORT (*n* = 95)	*P* value
Age	56 (51, 63)	56 (49, 62)	0.358
Sex			0.884
Female	53 (55.8)	55 (57.9)	
Male	42 (44.2)	40 (42.1)	
Smoking history	32 (33.7)	26 (27.4)	0.431
KPS			0.621
> 80	68 (71.6)	72 (75.8)	
≤ 80	27 (28.4)	23 (24.2)	
Tumor location			0.885
Left lung	45 (47.4)	47 (49.5)	
Right lung	50 (52.6)	48 (50.5)	
cT			0.083
1	46 (48.9)	33 (35.9)	
2	42 (44.7)	56 (60.9)	
3	6 (6.4)	3 (3.3)	
Missing data	3	3	
cN			0.667
0	50 (52.6)	47 (50.0)	
1	12 (12.6)	13 (13.8)	
2	28 (29.5)	32 (34.0)	
3	5 (5.3)	2 (2.1)	
Missing data	0	1	
pT			0.649
1	21 (22.1)	20 (21.5)	
2	64 (67.4)	58 (62.4)	
3	9 (9.5)	12 (12.9)	
4	1 (1.1)	3 (3.2)	
Missing data	0	2	
Positive lymph nodes			0.883
≤ 5	39 (41.1)	41 (43.2)	
> 5	56 (58.9)	54 (56.8)	
Cycles of chemotherapy			
< 4	11 (11.6)	7 (7.4)	0.446
4	76 (80.0)	83 (87.4)	
> 4	8 (8.4)	5 (5.3)	
Histology	61 (21.3)	22 (21.2)	0.368
Adenocarcinoma	91 (95.8)	94 (98.9)	
Others [a]	4 (4.2)	1 (1.1)	
EGFR mutations			0.281
19 del	44 (46.3)	50 (52.6)	
21 L858R	42 (44.2)	32 (33.7)	
Others [b]	9 (9.5)	13 (13.7)	
Surgery type			0.141
Open	45 (47.4)	34 (35.8)	
Thoracoscopic	50 (52.6)	61 (64.2)	
Adjuvant TKI	0 (0.0)	0 (0.0)	NA

Data are median (IQR) or n (%) unless otherwise specified. a, including adenosquamous carcinoma, large cell carcinoma and other rare histology types. b, including 18 exon, 20 exon and mixed mutations. IQR, interquartile range; KPS, Karnofsky performance status; cT, clinical T stage; cN, clinical N stage; pT, pathological T stage; TKI, tyrosine kinase inhibitors; NA, not available

EGFRm patients did not receive adjuvant TKI due to it not being recommended at the time. Lastly, the relatively limited sample size and follow-up period may result in insufficient events in certain outcomes, highlighting the need for randomized trials to further investigate these findings.

Conclusions

In conclusion, for completely resected pN2 Nsq-NSCLC receiving adjuvant chemotherapy, PORT may improve DFS in EGFRwt patients but has not been shown to improve it in EGFRm patients. These findings need to be validated through randomized controlled trials.

Abbreviations

PORT	Postoperative radiotherapy
DFS	Disease-free survival
Nsq-NSCLC	Non-squamous-cell non-small-cell lung cancer
EGFRm	EGFR-mutated
EGFRwt	EGFR wild-type
TKI	Tyrosine kinase inhibitors
LRFS	Locoregional relapse-free survival
DMFS	Distant metastasis-free survival
HR	Hazard ratio
OS	Overall survival
CI	Confidence interval
PSM	Propensity score matching
IQR	Interquartile range
NR	Not reached

Supplementary Information

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Supplementary Material 1

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None.

Author contributions

Y. Liu: conceptualization, resources, data curation, formal analysis, methodology, writing - original draft; Y. Men: resources, data curation, formal analysis, methodology, writing-original draft; X. Yang: validation, formal analysis; S. Sun: resources, methodology; Y. Bao: data curation, writing-review&editing; Z. Ma: resources; Y. Wang: formal analysis, methodology, investigation; Y. Zhai: methodology, software; J. Wang: resources, investigation, writing- review&editing; L. Deng: supervision, investigation; W. Wang: resources, investigation; N. Bi: supervision; writing- review&editing; L. Wang: supervision, investigation, writing- review&editing; Z. Hui: conceptualization, project administration; supervision; writing- review&editing.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding authors with reasonable request.

Declarations

Ethics approval and consent to participate
The institutional review boards approved this retrospective study and the requirement for informed consent was waived.

Consent for publication
All authors approved the final manuscript and the submission.

Competing interests
The authors declare no competing interests.

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