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Original Research Article

Is postoperative radiotherapy effective in patients with completely resected pathologic stage IIIA(N2) non-small cell lung cancer? High-risk populations should consider it

Shu-Xian Zhang [a,1], Chen-Chen Zhang [a,1], Run-Ping Hou [a], Xu-Wei Cai [a], Jun Liu [a], Wen Yu [a], Qin Zhang [a], Jin-Dong Guo [a], Chang-Lu Wang [a], Hong-Xuan Li [a], Zheng-Fei Zhu [b], Xiao-Long Fu [a,*], Wen Feng [a,*]

[a] Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

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ABSTRACT

Background and purpose: We aimed to assess the benefits of postoperative radiotherapy (PORT) in completely resected patients with pathologic stage IIIA(N2) non-small cell lung cancer (NSCLC) with a high risk of locoregional recurrence (LRR).

Materials and methods: A prospective, randomized trial was conducted starting in July 2016 to explore the optimal timing of PORT in high-LRR-risk patients with completely resected IIIA(N2) NSCLC (NCT02974426). Patients were identified as high-LRR-risk patients via the prognostic index (PI) model and were randomly assigned to PORT-first or PORT-last treatment. To evaluate PORT for high-LRR-risk patients, all patients in this trial constituted the PORT cohort, whereas high-LRR-risk patients without PORT were selected from a retrospective cohort as the non-PORT cohort. Propensity score-matched (PSM) analyses were conducted to compare overall survival (OS), disease-free survival (DFS), locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS).

Results: Between 2016 and 2022, 132 patients were included in the trial, with a median follow-up of 49.3 months. The 3-year OS rate was 83.2 %, and the 3-year DFS rate was 35.0 %. Among these patients, 122 patients (92 %) received planned PORT. For 132 intention-to-treat patients, PSM analysis with the non-PORT cohort (n = 307) resulted in 130 matched pairs. The results revealed that PORT improved LRFS (3-year LRFS, 77.6 % vs. 57.3 %; p = 0.00014), DFS (3-year DFS, 35.2 % vs. 28.6 %; p = 0.038), and OS (3-year OS, 83.0 % vs. 60.7 %; p = 0.00017), with no difference in DMFS (p = 0.17).

Conclusion: PORT could increase local control, DFS, and OS in high-LRR-risk patients with completely resected IIIA(N2) NSCLC. Future research should utilize multidimensional data to pinpoint more precise subgroups benefiting from PORT, with prospective trials validating these findings.

1. Introduction

Completely resected non-small cell lung cancer (NSCLC) patients with histologically confirmed IIIA(N2) disease constitute a heterogeneous population, encompassing those with incidentally discovered pathologic N2 (pN2) disease following complete surgery (IIIA-1, IIIA-2) and those recognized as N2 metastases by preoperative staging (IIIA-3) [1–3]. Locoregional recurrence (LRR) and distant metastases (DMs) following complete surgery remain significant issues for this population, necessitating a combined modality approach based on surgery [4]. Platinum-based postoperative chemotherapy (POCT) is routinely recommended [5]. More recently, studies have indicated that the use of

Abbreviations: PORT, postoperative radiotherapy; NSCLC, non-small cell lung cancer; LRR, locoregional recurrence; PI, prognostic index; PSM, propensity score-matched; OS, overall survival; DFS, disease-free survival; LRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival.

* Corresponding authors at: 241 West Huaihai Road, Shanghai 200030, China.
E-mail addresses: xlfu1743@shchest.org (X.-L. Fu), fengwen@shsmu.edu.cn (W. Feng).

[1] These authors contributed to the work equally and should be regarded as co-first authors.

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immune checkpoint inhibitors (ICIs) has improved the clinical benefit for patients with early-stage NSCLC (neoadjuvant or adjuvant) [6,7]. In addition, tyrosine kinase inhibitors (TKIs) have been evaluated as adjuvant treatments for IB-IIIA NSCLC patients with known alterations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) [8,9]. Despite these advancements in systemic therapies, studies of relapse patterns reveal that LRR continues to be a critical issue [7–9]. In the CheckMate 816 trial, LRR rates were recorded at 19 % in the ICI arm and 22 % in the chemotherapy arm [7].

Over the past two decades, advances in radiotherapy (RT) technology have reduced cardiopulmonary toxicity, and several studies have revealed that modern postoperative radiotherapy (PORT) might improve local control and overall survival (OS) in patients with pN2 NSCLC [10–15]. However, recent phase III trials, i.e., Lung ART and PORT-C, have indicated that not all patients with completely resected stage IIIA(N2) NSCLC benefit from PORT, and further research is needed to identify optimal populations that would benefit most from PORT [16–20].

To apply PORT selectively, it is crucial to identify high-LRR-risk factors. In previous studies, our team established optimal PORT clinical target volume (CTV) delineation guidelines and a prognostic index (PI) model for LRR risk assessment in completely resected IIIA(N2) NSCLC patients [21–25]. The proposed PORT CTV delineation guidelines define distinct CTVs for left-sided and right-sided lung cancers [21], and their safety and efficacy have subsequently been confirmed [22,23]. The PI model was built on the basis of 3 independent risk factors (heavy smoking history, clinical N2 status [cN2], and more than 4 positive lymph nodes [LNs]) to predict the effect of PORT [24,25]. Patients with a minimum of 2 risk factors can be stratified into the high-LRR-risk group [24,25]. On the basis of previous studies, we conducted a randomized clinical trial (NCT02974426) to explore the optimal timing of PORT for high-LRR-risk patients [26]. According to the statistical calculations, 1094 patients were expected to enrol in this trial. However, enrolment was delayed, and the number of eligible patients declined dramatically with the use of neoadjuvant or adjuvant novel systemic therapies (ICI or TKI). Consequently, this trial has been closed owing to insufficient accrual.

Despite the negative results of Lung ART and PORT-C, selective PORT application remains necessary for certain populations. The effect of PORT on high-LRR-risk populations is still unclear. In this study, we presented data from our prospective trial and compared them with those of a retrospective cohort using propensity score matching (PSM), aiming to clarify the value of PORT in high-LRR-risk populations.

2. Materials and methods

2.1. Study design and participants

2.1.1. The PORT cohort

We conducted this multicentre, prospective, randomized clinical trial (NCT02974426) starting in July 2016 in 5 hospitals in Shanghai, China, with the aim of investigating the optimal timing of PORT in completely resected stage IIIA(N2) NSCLC patients with a high risk of LRR [26]. This trial was approved by the institutional review board of our centre (KS1617).

Eligible patients were 18 years or older, had undergone complete resection (lobectomy or sleeve resection), and were pathologically diagnosed with T1-3N2M0 NSCLC (according to the TNM classification in the Union for International Cancer Control 7th edition [27]). Patients were required to have pathological N2 mediastinal nodal involvement following complete surgery. Complete resection was defined as microscopic tumour-free resection margins and systematic nodal assessment with at least three N2 stations sampled or completely dissected (including the subcarinal station) [28]. Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1. Patients who received neoadjuvant therapy, received adjuvant ICIs or TKIs, had simultaneous or sequential second primary cancers, or had uncontrolled active infection were excluded. Further details are available in the study protocol, which is included in the supplementary material.

Enrolment assessment occurred after the patients had undergone surgery. Before enrolment, all patients were required to undergo assessments to rule out metastatic disease, including chest computed tomography (CT) scans, brain enhanced magnetic resonance imaging (MRI) or enhanced CT, and abdominal ultrasound or CT. The presence of absence of pretreatment positron emission tomography-computed tomography (PET–CT) was a stratification factor in this study, but it was not a mandatory criterion for enrolment.

With the PI model, patients with at least two risk factors (heavy smoking history, cN2, and more than 4 positive LNs) can be classified into the high-LRR-risk group [24]. Heavy smokers are individuals who have a smoking history of more than 10 pack-years and/or who quit smoking less than 15 years ago, excluding those classified as never-smokers (fewer than 100 cigarettes in their lifetime) or light ex-smokers [29]. Patients with mediastinal LN enlargement on a preoperative CT scan ($\geq$10 mm in short-axis diameter) and a positive endobronchial ultrasound (EBUS) result, or those for whom EBUS was not performed, were considered to have cN2 lesions. The number of positive LNs was determined by summing the pathologically metastatic N1 and N2 nodes, as reported in the pathology findings.

High-LRR-risk patients were selected for enrolment according to the PI model ($\geq$2 risk factors for LRR) and randomly assigned (1:1) to Arm I (PORT-first treatment: [concurrent chemoradiotherapy + 2 cycles of sequential POCT] or [PORT + 4 cycles of sequential POCT]) or Arm II (PORT-last treatment: 4 cycles of POCT + sequential PORT). During concurrent chemoradiotherapy, 2 cycles of chemotherapy were given. For additional details, please refer to the attached study protocol. To assess the value of PORT for high-LRR-risk patients, we analysed the two arms in this trial as the PORT cohort (Fig. 1A).

2.1.2. The non-PORT cohort

We retrospectively reviewed the records of consecutive patients with pT1-3N2M0 NSCLC (TNM classification 7th ed.) who underwent complete resection at Shanghai Chest Hospital between 2012 and 2016, as published in our previous studies [24,25]. The non-PORT cohort was selected using almost the same criteria as in the prospective trial: complete resection through lobectomy or pneumonectomy, systematic mediastinal dissection or sampling with at least three N2 stations (including the subcarinal station) [28], pathologically stage IIIA(N2) NSCLC, postoperative follow-up $\geq$ 4 months, and no history of neoadjuvant therapy or receipt of adjuvant ICI or TKI. Patients who received adjuvant therapy were treated with platinum-based POCT. For this study, we selected patients who did not receive PORT and were at a high risk of LRR on the basis of the PI model to form the non-PORT cohort, and updated their recurrence and survival follow-up data (Fig. 1B). This retrospective study was approved by the institutional review board of our center.

2.2. Treatment

Patients in the prospective trial received 4 cycles of POCT (platinum-containing two-drug combinations). PORT was conducted via intensity-modulated radiotherapy (IMRT) with a linear accelerator with 6-MV X-rays. CTVs were delineated separately for left-sided (bronchial stump and LN stations 2R, 2L, 4R, 4L, 5, 6, 7, and 10 to 11L) and right-sided lung cancers (bronchial stump and LN stations 2R, 4R, 7, and 10 to 11R), following our institutional guidelines [21]. CTV was expanded by a 0.5–0.8 cm margin to create planning target volume (PTV)-C. The prescribed total PTV-C dose was 50.4 Gy, which was administered daily at 1.8 Gy per fraction for 5 days per week. In cases of pathological extracapsular node extension or cN2 disease with close anatomical proximity to the trachea and large bronchus or great vessels in the

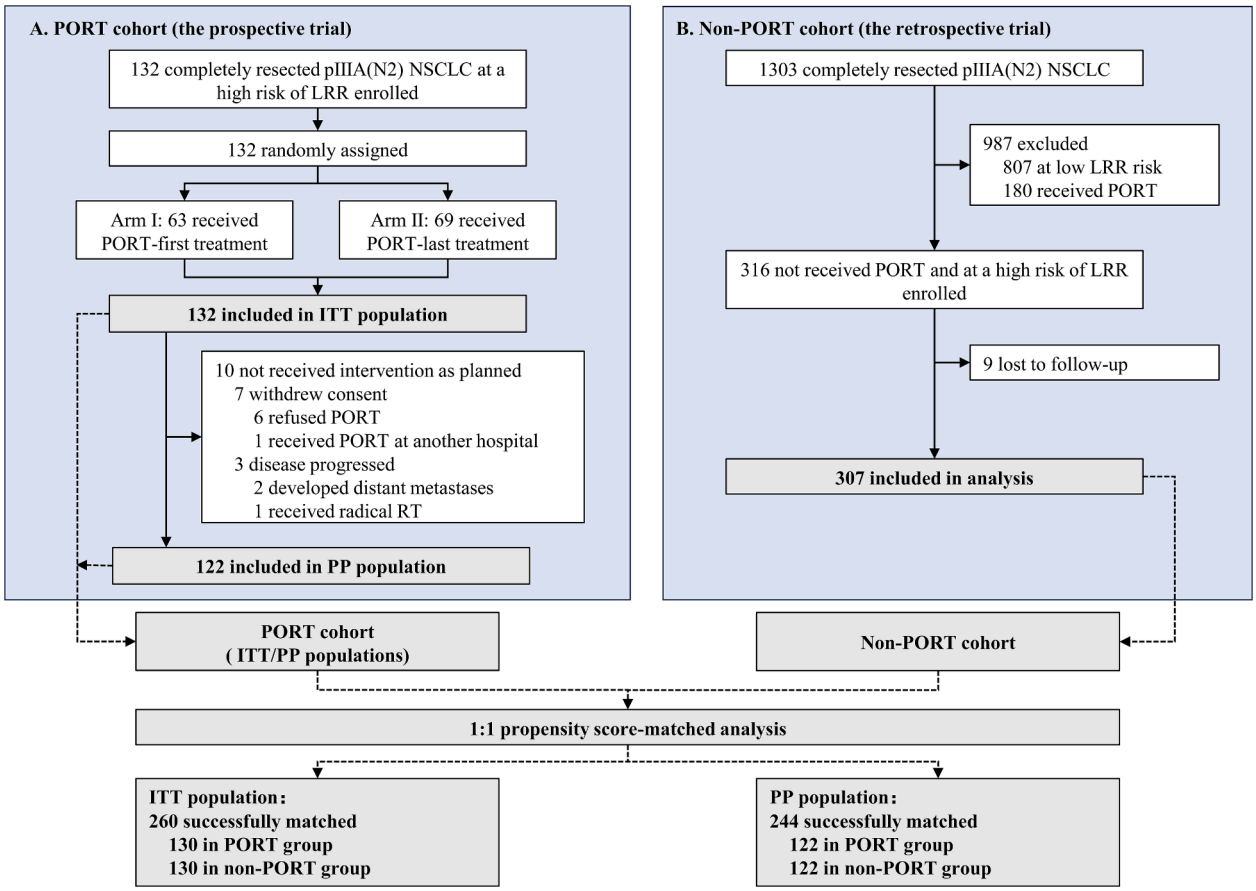

Fig. 1. Study schema. Flowchart showing selection of study population. pIIIA(N2) NSCLC, pathologic stage IIIA(N2) non-small cell lung cancer; LRR, locoregional recurrence; PORT, postoperative radiotherapy; ITT, intention-to-treat; PP, per-protocol; RT, radiotherapy.

preoperative CT scan, the lymph node stations with such findings were delineated as CTV-boost to account for the microscopic extension of nodal disease; then, a 0.5–0.8 cm margin was added to create PTV-boost, with the dose increased to 60.2 Gy. Doses were prescribed to the PTV, ensuring 95 % coverage of the prescription dose for 99 % of the PTV and 99 % coverage for 95 % of the PTV. The dose constraints for the surrounding organs were as follows: maximum spinal cord dose < 45 Gy; mean lung dose < 13 Gy; and lung volume receiving 20 Gy (V20) < 23 %; and mean heart dose < 30 Gy.

2.3. Follow-up and endpoints

All patients in the two cohorts underwent follow-up assessments every 3 months for the initial 24 months posttreatment, then every 6 months from 2 to 5 years, and annually thereafter. The follow-up assessments included clinical examinations, ECOG PS scores, laboratory tests, enhanced chest CT scans, abdominal ultrasonography, and enhanced brain MRI or CT.

OS was measured from surgery to death from any cause. DFS was defined as the time from surgery to recurrence or death. Locoregional recurrence-free survival (LRFS) was measured from surgery to LRR, whereas distant metastasis-free survival (DMFS) was defined from surgery to DM onset.

2.4. Statistics

The intention-to-treat (ITT) population of the PORT cohort included all eligible patients regardless of treatment adherence, whereas the per-protocol (PP) population included only those who followed the planned treatment. Univariate and multivariate analyses were performed to identify factors associated with LRFS, OS, DMFS, and DFS via the Cox model. Variables with $P < 0.2$ in the univariate analysis were further included in the multivariate analysis. For variable comparisons, *t* test, chi–squared test, and Mann–Whitney U tests were used. Kaplan–Meier analysis was used for survival analysis.

A 1:1 PSM was conducted to minimize the possible imbalances between groups. The matching variables included age, ECOG PS score, sex, smoking history, clinical N status, pathologic T stage, resection type, histology, number of positive LNs, and number of POCT cycles. After the calculating propensity scores were calculated, the nearest neighbour method was used to identify 1 non-PORT patient for each PORT patient, adopting a 0.05 match tolerance. A two-sided P value < 0.05 was considered statistically significant. R version 4.3.2 and SPSS version 27.0 were used for the analyses.

3. Results

3.1. Patients and characteristics of the PORT cohort

Between July 2016 and January 2022, a total of 132 eligible participants were included in the prospective trial, with 63 patients receiving PORT-first treatment and 69 receiving PORT-last treatment (Fig. 1A). The median follow-up for survivors was 49.3 months (range, 8.8–100.2). A total of 132 patients constituted the ITT population. Among these patients, 10 patients did not receive planned PORT, and 122 patients who completed the planned PORT constituted the PP population. The clinical features are summarized in Table 1. Ninety-five patients (72.0 %) were male, and 84 (63.6 %) were heavy smokers, with a median age of 60 years (range, 29–74 years). A total of 128 (97.0 %) patients underwent lobectomy resection; 92 (69.7 %) had pathologic

Table 1
Patient characteristics of the PORT cohort (ITT population, N = 132).

Variable	PORT Group N = 132(%)
Age at diagnosis, years	60 (29–74)
Median (range)	
Sex	
Female	37 (28.0)
Male	95 (72.0)
Smoking history*	
Never smoker/ Light smoker	48 (36.4)
Heavy smoker	84 (63.6)
ECOG PS score	
0	60 (45.5)
1	72 (54.5)
Clinical N status	
N0-1	18 (13.6)
N2	114 (86.4)
Pretreatment PET-CT	
Yes	78 (59.1)
No	54 (40.9)
Resection type	
Lobectomy	128 (97.0)
Sleeve resection	4 (3.0)
Tumor location	
Right upper lobe	39 (29.5)
Left upper lobe	29 (22.0)
Right middle lobe	4 (3.0)
Left lower lobe	24 (18.2)
Right lower lobe	32 (24.2)
Others	4 (3.0)
Tumor size	
≤3cm	67 (50.8)
>3, ≤5cm	52 (39.4)
>5, ≤7cm	10 (7.6)
>7cm	3 (2.3)
Pathologic T stage†	
T1	34 (25.8)
T2	69 (52.3)
T3-4	29 (22.0)
Pathologic N stage †	
N2a	40 (30.3)
N2b	92 (69.7)
No. of harvested LNs	
<15	66 (50.0)
≥15	66 (50.0)
No. of positive LNs	
≤4	38 (28.8)
>4	94 (71.2)
Percent of positive LNs	0.44 (0.04–1.00)
Median (range)	
Metastasis of skip N2 LNs	
Yes	21 (15.9)
No	111 (84.1)
Metastasis of subcarinal lymph node	
Yes	71 (53.8)
No	61 (46.2)
Metastasis of uppermost lymph nodes station	
Yes	98 (74.2)
No	34 (25.8)
Histology	
Adenocarcinoma	106 (80.3)
Squamous carcinoma	26 (19.7)
Histology grade	
Moderately differentiated	65 (49.2)
Poorly differentiated	67 (50.8)
Visceral pleura involved	
Yes	65 (49.2)
No	67 (50.8)
EGFR mutation status	
Detected	48 (36.4)
Not detected	84 (63.6)
ALK rearrangement status	
Detected	8 (6.1)
Not detected	124 (93.9)
POCT cycles	
<4	10 (7.6)
≥4	122 (92.4)
PORT timing	
PORT-first treatment	63 (47.7 %)
PORT-last treatment	69 (52.3 %)
Subsequent TKI treatment after recurrence	
Yes	50 (37.9)
No	82 (62.1)

Note: *Smoking history was categorized as never/light ex-smokers (<100 cigarettes smoked in their lifetime or ≤ 10 pack-years, having stopped for ≥ 15 years) or current/heavy ex-smokers.
†Pathologic T stage and N stage were according to the TNM classification in the Union for International Cancer Control 9th edition.
PORT, postoperative radiotherapy; ITT population, intent-to-treat population; ECOG PS score, Eastern Cooperative Oncology Group performance status score; PET-CT, positron emission tomography-computed tomography; no., the number; LNs, lymph nodes; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; POCT, postoperative chemotherapy; TKI, tyrosine kinase inhibitor.

N2b stage; 94 (71.2 %) had more than 4 positive LNs; 106 (80.3 %) had adenocarcinoma; and 48 (36.4 %) had EGFR mutations. A total of 122 patients (92.4 %) received 4 cycles of POCT, with only 10 patients receiving fewer cycles because of patient refusal.

3.2. Survival outcomes and adverse events in the PORT cohort

In the PORT cohort (N = 132), 42 patients died, and the median OS (mOS) was not reached. The 3-year OS rate was 83.2 %, and the 5-year OS rate was 58.6 %. The median DFS (mDFS) was 22.6 months. The 3-year DFS rate was 35.0 %, and the 5-year DFS rate was 29.6 %. Among the 87 patients who experienced relapse, 11 (12.6 %) had LRR as the first event, 65 (74.7 %) had DM, and 11 (12.6 %) had both LRR and DM. The LRFS rates were 76.9 % and 72.5 % at 3 and 5 years, respectively. The 3-year DMFS rate was 39.1 %, and the 5-year DMFS rate was 34.4 %.

Univariate and multivariate analyses of the prognostic factors for LRFS, OS, DMFS, and DFS were performed on the PORT cohort (Table 2 and Table S1). The number of positive LNs independently influenced LRFS (HR 3.76, 95 %CI 1.08–13.06, p = 0.037). The number of POCT cycles was an independent predictor of OS (HR 0.41, 95 %CI 0.17–0.99, p = 0.046), DMFS (HR 0.41, 95 %CI 0.18–0.96, p = 0.039), and DFS (HR 0.38, 95 %CI 0.16–0.89, p = 0.026). No significant difference was found between the PORT-first group and the PORT-last group.

No severe RT-related adverse events were observed in the PORT cohort. Only 3 patients (2.3 %) experienced grade 3 radiation pneumonitis, and 54 patients (40.9 %) experienced grade 1–2 radiation pneumonitis or radiation esophagitis. Among the 42 deaths recorded in the PORT cohort up to the last follow-up, 38 (90.5 %) were due to disease relapses and metastases. Additionally, 1 patient (2.4 %) died from a second primary thymus cancer, 2 patients (4.8 %) from Coronavirus Disease 2019 (COVID–19), and the cause of 1 death (2.4 %) remained unknown.

3.3. Non-PORT cohort and PSM analysis

The non-PORT cohort consisted of 316 high-LRR-risk patients without PORT (Fig. 1B). These patients were selected from a retrospective cohort at Shanghai Chest Hospital between 2012 and 2016. After excluding 9 patients due to loss of follow-up, 307 patients were included in the non-PORT cohort. The median follow-up time for survivors was 91.9 months (range 5.1–141.6).

A PSM analysis was conducted between the ITT population of the PORT cohort and the non-PORT cohort. The 1:1 matching resulted in 130 matched pairs with a total population of 260 patients and demonstrated satisfactory balance, with no significant differences in clinical or

Table 2
Univariate and multivariate analysis of factors affecting LRFS and OS among the PORT cohort (ITT population, N = 132).

Variable	LRFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95 %CI)	P	HR (95 %CI)	P	HR (95 %CI)	P	HR (95 %CI)	P
Age at diagnosis		0.06		0.143		0.877		
≤60 years	1		1		1			
>60 years	0.50 (0.24–1.03)		0.57 (0.27–1.21)		0.95 (0.52–1.7)			
Sex		0.808				0.804		
Female	1				1			
Male	1.10 (0.51–2.38)				1.09 (0.56–2.00)			
Smoking history*		0.589				0.718		
Never/ Light smoker	1				1			
Heavy smoker	0.82 (0.41–1.67)				0.89 (0.48–1.6)			
Clinical N status		0.371				0.469		
N0-1	1				1			
N2	0.67 (0.27–1.62)				1.46 (0.52–4.10)			
Resection type		0.947				0.263		
Lobectomy	1				1			
Sleeve resection	1.07 (0.15–7.86)				2.26 (0.54–9.40)			
Pathologic T stage †		0.444				0.437		
T1	1				1			
T2	0.64 (0.30–1.40)	0.265			1.52 (0.69–3.39)	0.299		
T3-4	0.57 (0.21–1.54)	0.268			1.04 (0.40–2.70)	0.943		
Pathologic N stage †		0.269				0.885		
N2a	1				1			
N2b	1.60 (0.69–3.71)				0.95 (0.49–1.80)			
No. of harvested LNs		0.253				0.49		
<15	1				1			
≥15	1.51 (0.75–3.06)				1.24 (0.67–2.30)			
No. of positive LNs		0.013		0.037		0.811		
≤4	1		1		1			
>4	4.48 (1.36–14.71)		3.76 (1.08–13.06)		1.09 (0.55–2.10)			
Metastasis of skip N2 LNs		0.901				0.098		0.134
Yes	1				1		1	
No	1.06 (0.41–2.76)				2.70 (0.83–8.74)		2.47 (0.76–8.04)	
Metastasis of uppermost LNs station		0.194		0.514		0.243		
Yes	1		1		1			
No	0.53 (0.20–1.38)		0.72 (0.27–1.93)		1.48 (0.77–2.85)			
Histology		0.141		0.734		0.527		
Adenocarcinoma	1		1		1			
Squamous carcinoma	0.41 (0.12–1.35)		0.81 (0.23–2.80)		1.27 (0.61–2.60)			
Histology grade		0.979				0.596		
Moderately differentiated	1				1			
Poorly differentiated	1.01 (0.5–2.02)				0.84 (0.45–1.50)			
Visceral pleura involved		0.452				0.245		
Yes	1				1			
No	1.30 (0.65–2.63)				0.70 (0.38–1.29)			
POCT cycles		0.486				0.025		0.046
<4	1				1		1	
≥4	2.02 (0.28–14.88)				0.37 (0.16–0.80)		0.41 (0.17–0.99)	
PORT timing		0.162		0.184		0.759		
PORT-first treatment	1		1		1			
PORT-last treatment	1.65 (0.82–3.35)		1.62 (0.80–3.29)		0.91 (0.50–1.67)			
Enrollment time period		0.695				0.906		
2015–2017	1				1			
2018–2022	0.86 (0.40–1.84)				0.96 (0.50–1.85)			

Note: * Smoking history was categorized as never/light ex-smokers (<100 cigarettes smoked in their lifetime or ≤ 10 pack-years, having stopped for ≥ 15 years) or current/heavy ex-smokers.
†Pathologic T stage and N stage were according to the TNM classification in the Union for International Cancer Control 9th edition.
LRFS, locoregional recurrence free survival; OS, overall survival; PORT, postoperative radiotherapy; ITT population, intent-to-treat population; no., the number; LNs, lymph nodes; POCT, postoperative chemotherapy.

pathological variables (Table 3). Similarly, the PP population in the PORT cohort was successfully matched with that in the non-PORT cohort via PSM analysis. After matching, the population comprised 244 patients, and the characteristics were well balanced (Table S2). The POCT cycles were balanced (Table S3).

3.4. Survival outcomes between the matched PORT and non-PORT groups

After PSM, survival outcomes were compared between the PORT and non-PORT groups. The matching results of the ITT population revealed that PORT significantly improved LRFS (3-year LRFS, 77.6 % for PORT vs. 57.3 % for non-PORT; p = 0.00014) (Fig. 2A), whereas no significant difference was detected in DMFS (3-year DMFS, 39.5 % for PORT vs. 39.1 % for non-PORT; p = 0.17) (Fig. 2B). DFS significantly improved in the PORT group (3-year DFS, 35.2 % for PORT vs. 28.6 % for non-PORT; p = 0.038), with an mDFS of 22.0 months (95 %CI, 14.8–29.2 months) compared with 18.9 months (95 %CI, 16.4–21.4 months) in the non-PORT group (Fig. 2C). The PORT group exhibited a significantly improved OS (3-year OS, 83.0 % vs. 60.7 %; p = 0.00017). The mOS was 43.3 months in the non-PORT group (95 %CI, 34.8–51.8 months) and

Table 3
Patient characteristics in matched and unmatched groups with the PORT group of ITT population.

Variable	Before PSM			After PSM		
	PORT Group N = 132(%)	Non-PORT Group N = 307(%)	P	PORT Group N = 130(%)	Non-PORT Group N = 130(%)	P
Age at diagnosis						
≤60 years	68 (51.5)	150 (48.9)	0.61	67 (51.5)	65 (50.0)	0.894
>60 years	64 (48.5)	157 (51.1)		63 (48.5)	65 (50.0)	
Sex						
Female	37 (28.0)	55 (17.9)	0.017	36 (27.7)	39 (30.0)	0.681
Male	95 (72.0)	252 (82.1)		94 (72.3)	91 (70.0)	
Smoking history*						
Never smoker/ Light smoker	48 (36.4)	73 (23.8)	0.007	47 (36.2)	46 (35.4)	0.897
Heavy smoker	84 (63.6)	234 (76.2)		83 (63.8)	84 (64.6)	
ECOG PS score						
0	60 (45.5)	136 (44.3)	0.823	59 (45.4)	58 (44.6)	0.901
1	72 (54.5)	171 (55.7)		71 (54.6)	72 (55.4)	
Clinical N status						
N0-1	18 (13.6)	30 (9.8)	0.006	18 (13.8)	21 (16.2)	0.602
N2	114 (86.4)	256 (83.4)		112 (86.2)	109 (83.8)	
unknown	0 (0.0)	21 (6.8)				
Pretreatment PET-CT						
Yes	78 (59.1)	219 (71.3)	0.012	76 (58.5)	90 (69.2)	0.071
No	54 (40.9)	88 (28.7)		54 (41.5)	40 (30.8)	
Resection type						
Pneumonectomy	0 (0.0)	40 (13.0)	<0.001	0 (0.0)	4 (3.1)	0.061
Lobectomy	128 (97.0)	247 (80.5)		126 (96.9)	118 (90.8)	
Sleeve resection	4 (3.0)	20 (6.5)		4 (3.1)	8 (6.2)	
Tumor location						
Right upper lobe	39 (29.5)	99 (32.2)	0.53	38 (29.2)	48 (36.9)	0.245
Left upper lobe	29 (22.0)	71 (23.1)		29 (22.3)	31 (23.8)	
Right middle lobe	4 (3.0)	15 (4.9)		4 (3.1)	7 (5.4)	
Left lower lobe	24 (18.2)	39 (12.7)		23 (17.7)	13 (10.0)	
Right lower lobe	32 (24.2)	67 (21.8)		32 (24.6)	30 (23.1)	
Others	4 (3.0)	16 (5.2)		4 (3.1)	1 (0.8)	
Pathologic T stage†						
T1	34 (25.8)	57 (18.6)	0.229	34 (26.2)	27 (20.8)	0.564
T2	69 (52.3)	179 (58.3)		68 (52.3)	75 (57.7)	
T3-4	29 (22.0)	71 (23.1)		28 (21.5)	28 (21.5)	
No. of harvested LNs						
<15	66 (50.0)	176 (57.3)	0.157	65 (50.0)	80 (61.5)	0.061
≥15	66 (50.0)	131 (42.7)		5 (50.0)	50 (38.5)	
No. of positive LNs						
≤4	38 (28.8)	105 (34.2)	0.267	38 (29.2)	39 (30.0)	0.892
>4	94 (71.2)	202 (65.8)		92 (70.8)	91 (70.0)	
Percent of positive LNs Median (range)	0.44 (0.04–1.00)	0.44 (0.03–1.00)	0.721	0.45 (0.04–1.00)	0.46 (0.06–1.00)	0.444
Histology						
Adenocarcinoma	106 (80.3)	197 (64.2)	<0.001	105 (80.8)	108 (83.1)	0.629
Non-adenocarcinoma	26 (19.7)	110 (35.8)		25 (19.2)	22 (16.9)	
POCT cycles						
<4	10 (7.6)	96 (31.3)	<0.001	9 (6.9)	12 (9.2)	0.495
≥4	122 (92.4)	211 (68.7)		121 (93.1)	118 (90.8)	

Note: *Smoking history was categorized as never/light ex-smokers (<100 cigarettes smoked in their lifetime or ≤ 10 pack-years, having stopped for ≥ 15 years) or current/heavy ex-smokers.
†Pathologic T stage was according to the TNM classification in the Union for International Cancer Control 9th edition.
ITT population, intent-to-treat population; PORT, postoperative radiotherapy; PSM, propensity score matching; ECOG PS score, Eastern Cooperative Oncology Group performance status score; PET-CT, positron emission tomography-computed tomography; no., the number; LNs, lymph nodes; POCT, postoperative chemotherapy.

was not reached in the PORT group.

The matched results for the PP population were consistent (Fig. S1). PORT significantly improved LRFS (3-year LRFS, 78.7 % for PORT vs. 61.2 % for non-PORT; p = 0.00028), DFS (3-year DFS, 35.3 % for PORT vs. 30.2 % for non-PORT; p = 0.027), and OS (3-year OS, 84.5 % for PORT vs. 61.8 % for non-PORT; p < 0.0001) but not DMFS (3-year DMFS, 38.9 % for PORT vs. 41.2 % for non-PORT; p = 0.16).

4. Discussion

In our previous studies, we developed a PI model to estimate postoperative LRR risk in completely resected stage IIIA(N2) patients and applied it to a large sample size in a validation cohort to demonstrate its efficacy in a real-world setting [24]. Using this PI model, our retrospective analysis indicated that PORT may improve local control and improve survival for high-LRR-risk patients [24,25]. Therefore, PORT should be considered for high-LRR-risk patients based on our previous studies, and further exploration is needed to determine its optimal sequence. Additionally, we explored the optimal PORT CTV delineation for right- and left-sided lung cancer in pN2 disease, which proved safe and effective [21–23]. On the basis of these findings, we initiated a randomized trial to investigate the optimal timing of PORT for high-LRR-risk patients with completely resected IIIA(N2) disease [26]. However, enrolment was slow with the use of neoadjuvant or adjuvant ICIs and TKIs. Between July 2016 and January 2022, 132 patients were included in this trial, and 122 patients received planned PORT. Given the results of Lung ART and PORT-C, determining which populations would benefit from PORT is critical. Therefore, we

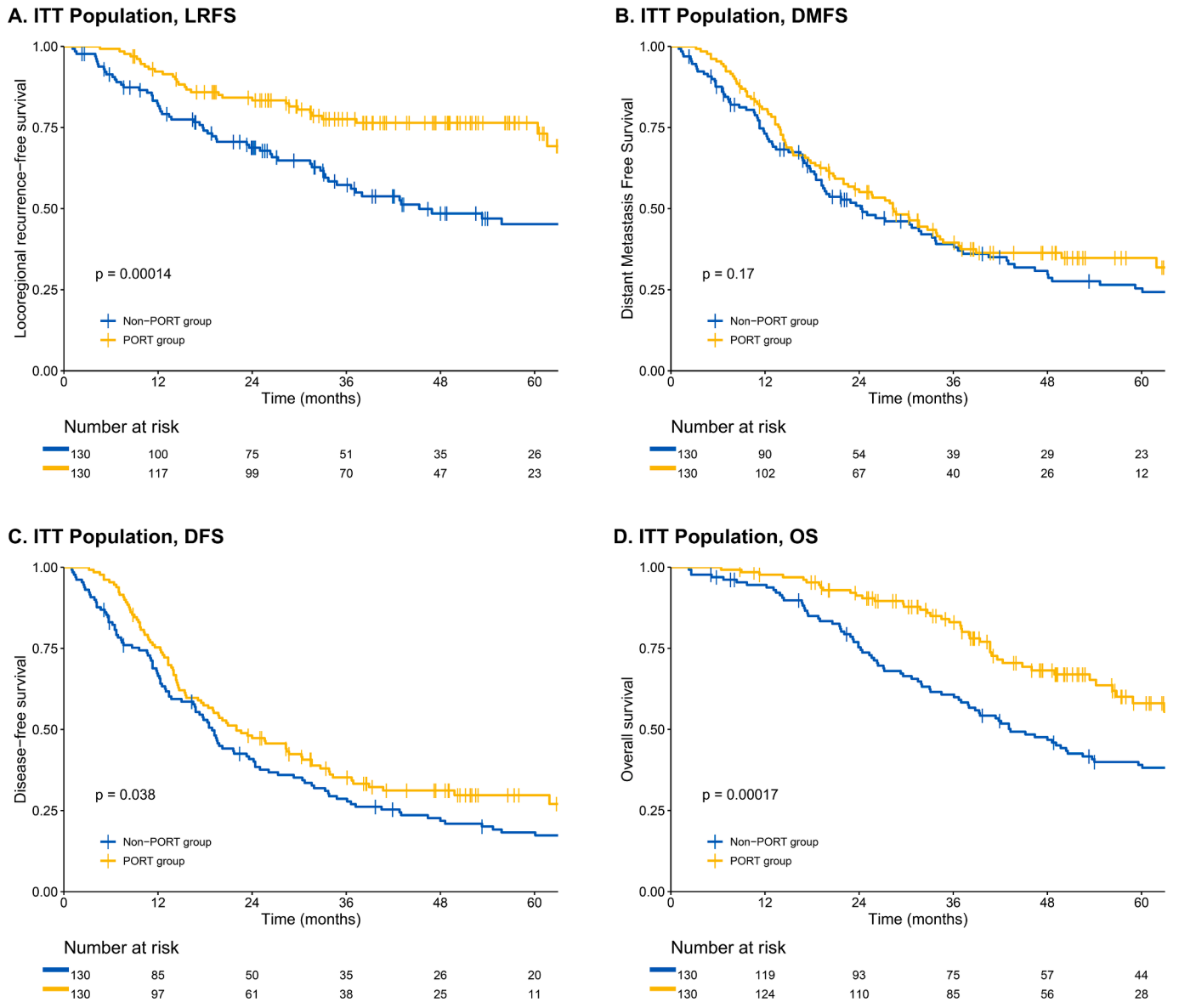

Fig. 2. Kaplan-Meier analysis among patients with PORT or not using intention-to-treat population (ITT population). A, locoregional recurrence-free survival (LRFS); B, distant metastasis-free survival (DMFS); C, disease-free survival (DFS); D, overall survival (OS).

presented the data from our prospective trial and compared them with those of a high-LRR-risk retrospective cohort without PORT after conducting PSM. The results demonstrated that high-LRR-risk patients with completely resected stage IIIA(N2) NSCLC could benefit from PORT, including improvements in OS, DFS, and LRFS. These findings support the use of PORT in high-LRR-risk subgroups.

Two prospective randomized phase III studies, Lung ART and PORT-C, questioned the standard use of PORT for patients with completely resected stage IIIA(N2) NSCLC [16,17]. However, certain aspects of these studies remain debatable. First, in Lung ART, 89 % of patients received 3D-CRT, potentially influencing OS due to RT-induced cardiopulmonary toxicity. Notably, 16 % of deaths in the PORT group were attributed to cardiopulmonary disease. Second, in PORT-C, 44 patients (23.9 %) refused PORT, and only 76.1 % were protocol adherent in the PORT group. The PP analysis indicated an improvement in DFS in the PORT group ($p = 0.05$). Third, both Lung ART and PORT-C included patients with pathologic N2 mediastinal nodal involvement after complete resection. However, the pathologically confirmed IIIA(N2) NSCLC may be a heterogeneous group, necessitating the identification of a precise subgroup of patients for whom PORT may be beneficial. A stratified analysis of PORT-C based on the number of detected and positive LNs indicated significant differences in DFS ($p = 0.04$), emphasizing the need for careful patient selection [18–20]. To our knowledge, the PORT cohort in our study is the only prospective investigation for PORT in completely resected stage IIIA(N2) patients with high risk of LRR.

In addition, we compare the PORT cohort from our prospective trial with those from the Lung ART and PORT-C trials [16,17], focusing on the target populations, efficacy outcomes, and safety profiles. First, regarding the enrolled populations, our study included pathologic stage IIIA(N2) patients who may have an increased risk of LRR as identified by our PI model [24]. The percentage of cN2 disease in our PORT cohort was 86.4 %, whereas it was 43.5 % in PORT-C and 57.5 % in Lung ART. Moreover, 71.2 % of our PORT cohort had more than 4 positive LNs, higher than the 61.4 % in the PORT-C group with 4 or more positive LNs. Second, in terms of the efficacy of PORT, LRFS significantly differed between the two groups in our study, consistent with the findings from both PORT-C and Lung ART [17,30]. These studies collectively demonstrated the ability of PORT to improve local control [10,17,31]. The 3-year OS rate in our study was comparable to that of PORT-C. Our

study revealed relatively decreased DMFS and DFS rates, possibly because we focused on higher-LRR-risk patients. However, using PSM analyses in our study, we found that PORT not only improved local control but also translated to significant DFS and OS benefits in this high-LRR-risk patient group. Third, regarding the safety of PORT, the percentage of noncancer-related deaths in our PORT cohort (9.5 %) was consistent with that in the PORT group in the PORT-C trial (6.0 %), while 16 % of the PORT group in the Lung ART trial died from cardiopulmonary causes.

In this study, PORT effectively reduced LRR in completely resected stage IIIA(N2) patients with a high risk of LRR, potentially leading to an OS benefit. Our results also suggested a DFS benefit from PORT for this group. However, there was no significant difference in DMFS. DM represented the most common failure pattern in the PORT cohort, with a 3-year cumulative incidence of 56.8 %. The cumulative incidence of brain metastases reached 20.5 %. Therefore, effective management of DMs, particularly in patients at high risk of brain metastases, is crucial for improving both survival outcomes and the quality of life. Additionally, PORT may provide greater benefits to a specific subgroup of pN2 patients at a high risk of LRR but a low risk of DM, necessitating the need for more precise prognostic predictions [25]. In the era of the advancements in targeted and immunotherapies, which have reduced the risk of DMs, LRR has become a more pronounced concern [7–9]. This shift underscores the challenges in identifying high-risk populations for PORT within the context of evolving systematic therapies [32].

For screening the high-LRR-risk population, we used the criteria of heavy smoking history, cN2 status, and more than 4 positive LNs [24]. Existing studies have focused primarily on pathologic LN status when identifying potential PORT candidates [33,34]. Several retrospective studies have indicated that patients with cN2 status, multiple station N2 involvement, or a relatively high lymph node ratio might benefit from PORT in terms of survival [31,35–39]. The assessment of the populations that would benefit from PORT is still inconclusive. Thus, in this study, we proposed a PI model and demonstrated its utility in guiding PORT for high-LRR-risk populations, serving as a reference for clinical practice.

This study has two major advantages. First, the PORT cohort in our study was derived from a prospective cohort, tailored specifically for patients who had undergone complete resection of stage IIIA(N2) NSCLC and were identified as having a high risk of LRR. The LRR risks were evaluated via our previously validated PI model, which is a standardized screening criterion that is based on clinicopathologic features related to LRR [24,25]. Second, all patients received PORT following our institutional CTV delineation guidelines, which were designed on the basis of comprehensive surgical and radiographic evidence [40–42]. Given the relationship between radiation volume and RT-induced mortality [43], our proposed PORT CTV was designed based on comprehensive surgical and radiographic evidence [21].

This study has several limitations. First, conclusions were drawn by matching our prospective trial patients with a retrospective cohort, which may have resulted in unknown selection bias and inconsistent follow-up intervals. We attempted to minimize selectivity bias via PSM analysis. Second, a discrepancy exists in the enrolment periods between the two groups, mainly due to recent advances in neoadjuvant therapies that have decreased the proportion of patients undergoing direct surgery, thereby reducing the pool of comparable patients available for PSM post-2016. Considering the potential influence of advances in diagnostic and therapeutic approaches, we employed PSM to balance the confounders, including the use of PET–CT and the number of POCT cycles. No patients in either group received neoadjuvant therapies, adjuvant ICIs, or adjuvant TKIs. Although exposure to subsequent relapse therapy may influence OS analysis, its impact on DFS appears minimal. Third, high-LRR-risk populations were identified on the basis of our predictive models built with clinicopathological variables. Emerging technologies such as artificial intelligence and liquid biopsy, coupled with multidimensional information from CT scans, pathology H&E images, and biomics information, might improve model accuracy and robustness [44]. Multicentre validation with large sample sizes and model optimization based on multidimensional information are still needed. Finally, as novel systemic drug regimens (targeted or immunotherapies) have entered the perioperative arena, the DFS of patients with stage III NSCLC after complete resection has improved significantly [6,9]. However, the observed decrease in the LRR rate following the administration of these novel systemic therapeutic agents has not achieved the desired clinical outcomes [7–9]. Therefore, future research should explore the value and optimal integration of PORT with targeted or immunotherapies, aiming to discern the synergistic effects and potential benefits of such combined treatment modalities.

5. Conclusions

In this study, the PSM analysis of PORT for high-LRR-risk patients with completely resected stage IIIA(N2) NSCLC revealed that PORT significantly improved LRFS, DFS, and OS but not DMFS. This indicates the importance of refining the profile of appropriate candidates for PORT. Future research should use multidimensional data to more precisely identify patient subgroups that may benefit from PORT, and prospective trials should be planned to validate these results, especially in the current era of comprehensive perioperative treatments.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100889.

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