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Postoperative radiotherapy option based on mediastinal lymph node reclassification for patients with pN2 non-small-cell lung cancer

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ABSTRACT

Background In this research, we used the mediastinal lymph node reclassification proposed by the International Association for the Study of Lung Cancer (IASLC) to screen for patients with pathologic N2 (pN2) non-small-cell lung cancer (NSCLC) who might benefit from postoperative radiotherapy (PORT).

Methods The study enrolled 440 patients with pN2 NSCLC who received complete surgical resection and allocated them to one of three groups: N2a1 (single-station skip mediastinal lymph node metastasis), N2a2 (single-station non-skip mediastinal lymph node metastasis), and N2b (multi-station mediastinal lymph node metastasis). Rates of local recurrence at first recurrence in patients receiving and not receiving PORT were compared using the chi-square test. Overall (OS) and disease-free survival (DFS) were then compared using Kaplan–Meier survival analysis with log-rank test. In addition, the factors potentially influencing OS and DFS were analyzed using univariate and multivariate Cox regression.

Results The rate of local recurrence for the N2a2 and N2b groups was significantly lower in patients receiving PORT ($p = 0.044$ and $p = 0.043$ respectively). The log-rank test revealed that, for the N2a1 group, differences in OS and DFS were not statistically significant between the patients who did and did not receive PORT ($p = 0.304$ and $p = 0.197$ respectively). For the N2a2 group, OS and DFS were markedly superior in patients who received PORT compared with those who did not ($p = 0.001$ and $p = 0.014$ respectively). For the N2b group, OS was evidently better in patients who received PORT compared with those who did not ($p = 0.025$), but no statistically significant difference in DFS was observed ($p = 0.134$). Multivariate regression analysis revealed that, in the N2a1 group, PORT was significantly associated with poor OS [hazard ratio (HR): 2.618; 95% confidence interval (CI): 1.185 to 5.785; $p = 0.017$]; in the N2a2 group, PORT was associated with improved OS (HR: 0.481; 95% CI: 0.314 to 0.736; $p = 0.001$) and DFS (HR: 0.685; 95% CI: 0.479 to 0.980; $p = 0.039$).

Conclusions For patients with pN2 NSCLC who receive complete resection, PORT might be beneficial only for patients with single-station non-skip metastasis (N2a2). Patients with single-station skip metastasis (N2a1) and multi-station metastasis (N2b) might not currently benefit from PORT.

Key Words Non-small-cell lung cancer, International Association for the Study of Lung Cancer, mediastinal lymph node skip metastasis, mediastinal lymph node stations

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers, and approximately 30% of affected patients have locally advanced disease at the time of diagnosis[1]. For patients with resectable NSCLC at stages IIIA and IIIB (N2), evidence is sufficient to verify that postoperative chemotherapy (POCT) is beneficial for survival[2,3]. However, whether postoperative radiotherapy (PORT) can improve the prognosis for those patients remains controversial.

A meta-analysis performed in 1998 suggested that PORT could not significantly improve the postoperative survival

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of patients with pN2 NSCLC[4], which at the time reduced the clinical application of PORT[5]. However, the meta-analysis was also disputable because of its inclusion of outdated studies, older radiotherapy (RT) techniques, and incomplete surgical information. Subsequently, some studies verified that, with modern RT techniques, PORT is sufficiently safe[6] and can improve the postoperative survival of patients with pN2 NSCLC[5,7,8]. However, some scholars have held the opposite opinion[9,10], making it crucially important to screen for patients who might benefit from PORT.

Some studies have attempted to screen patients using mediastinal lymph node (LN) metastasis as reported in postoperative pathology reports[11–13], but no effective and universally applicable method has been put forward so far. Before the release of the latest TNM classification, the International Association for the Study of Lung Cancer (IASLC) proposed revisions to the existing N classification for patients with NSCLC, and the effectiveness of the change in predicting prognosis has been confirmed[14,15]. However, the new classification has not been applied to guide postoperative treatment. For the present study, we reclassified patients with completely resected pN2 NSCLC based on mediastinal LN status (with reference to the revised N classification from the IASLC), and we analyzed the subgroups to determine which patients might benefit from PORT.

METHODS

Patient Selection

Patients with NSCLC treated from January 2009 through December 2016 were selected from the medical record system of Zhejiang Cancer Hospital (Hangzhou, P.R.C.) based on these inclusion criteria:

- The patient underwent surgery in our hospital and had a complete postoperative pathology report, with confirmation of pT1–4N2M0 (IIIA, IIIB) NSCLC according to the 8th edition of the American Joint Committee on Cancer TNM classification.
- The patient underwent lobectomy or ipsilateral pneumonectomy with a negative surgical margin (R0).

That search retrieved 619 patients. Subsequently, patients were further screened using these criteria:

- The patient underwent systemic intrapulmonary and mediastinal LN dissection, with 6 or more LNs having been biopsied[16].
- The patient received no neoadjuvant radiotherapy or chemoradiotherapy, but did receive at least 1 cycle of chemotherapy after surgery.
- If the patient received PORT, the total RT dose was at least 48.0 Gy.
- The patient had a preoperative Eastern Cooperative Oncology Group performance status of 0–1.
- The patient was subsequently followed for at least 3 months from the date of surgery.

After application of the foregoing criteria, the study enrolled 440 patients. All patients underwent surgery and pathology examination of surgical specimens at Zhejiang Cancer Hospital.

Mediastinal LN Reclassification

With reference to the IASLC suggestions, mediastinal LN metastasis was used to classify patients with pN2 NSCLC as N2a1 (single-station skip metastasis), N2a2 (single-station non-skip metastasis), or N2b (multi-station metastasis). Typically, "skip metastasis" refers to mediastinal LN metastasis with no intrapulmonary or hilar (N1) LN metastasis[17]. In addition, for this paper, we defined the LN ratio (LNR) as the total number of positive LNs divided by the total number of biopsied LNs.

PORT

Implementation of PORT was decided by thoracic surgeons and thoracic radiation oncologists. Patients were divided into PORT and non-PORT groups according to whether they had received PORT. In line with the definition of "lymph node area" by the IASLC[17], the clinical target volume in right lung cancer included the 2R, 4R, 7, and 10R areas and the surgical stump; in left lung cancer, it included the 2R, 2L, 4R, 5–7, and 10L areas and the surgical stump. The planning target volume was defined as an expansion of the clinical target volume by 0.6–0.8 cm. The prescription dose was defined as 95% of the dose delivered to the planning target volume, with a less than 5% difference in internal target dose uniformity and an internal target maximum dose of 110% or less. The total normal lung volume receiving 20 Gy or less was defined as less than 25%; the mean lung dose was less than 13 Gy; the maximum dose to spinal cord was less than 45 Gy; the total normal heart volume receiving 40 Gy was less than 50%; and the mean heart dose was 30 Gy or less. Radiotherapy was delivered as X-rays (6 MV) at 1.8–2 Gy per fraction once daily for 5 days per week, to a total dose of 48.0–60.0 Gy and a median dose of 50.0 Gy. Of the patients who received PORT, 40 were treated with 3-dimensional conformal RT, and 183 were treated with intensity-modulated RT.

POCT

For patients with pN2 NSCLC, POCT is included in the U.S. National Comprehensive Cancer Network guidelines per type I evidence[18], and therefore the 440 enrolled patients all received POCT for 1–6 cycles (median: 4 cycles). Most chemotherapy regimens were platinum-based doublets, among which the platinum used was either intravenous cisplatin (25 mg/m^2 on days 1 and 8) or intravenous carboplatin (area under the curve 5 on day 1). Doublets included intravenous vinorelbine (25 mg/m^2 on days 1 and 8) plus platinum (71 patients, 16.1%); intravenous gemcitabine (1000 mg/m^2 on days 1–3) plus platinum (164 patients, 37.3%); intravenous pemetrexed (500 mg/m^2 on day 1) plus platinum (117 patients, 22.6%); and intravenous paclitaxel (135–175 mg/m^2 on day 1) plus platinum (77 patients, 17.5%). Other regimens were used in 11 patients (2.5%).

Follow-Up

Patients were followed by telephone or outpatient visit once every 3 months during the first 2 years after treatment, once every 6 months in years 2–5 after treatment, and once every 12 months thereafter. The conventional outpatient follow-up included a medical history and physical

examination; hematologic examination; and chest and upper abdomen computed tomography, brain magnetic resonance imaging, radionuclide bone imaging, and integrated positron-emission tomography–computed tomography when necessary. Local recurrence was defined as disease relapse at the bronchus stump, ipsilateral hilum, or mediastinum; all other sites of failure, including the supraclavicular fossa and contralateral hilum, were considered distant metastasis[19]. The diagnosis of disease recurrence was based on imaging or histopathologic evidence.

Statistical Analysis

The clinicopathologic features of the PORT and the non-PORT groups were compared using the chi-square test. The overall recurrence rate (local recurrence and distant metastasis) at first recurrence was defined as the number of patients with local recurrence or distant metastasis as their first recurrence pattern divided by the total number of patients, compared between the PORT and the non-PORT groups using the chi-square test. Overall survival (OS) was defined using the date of death from any cause or of last follow-up from the date of surgery. Disease-free survival (DFS) was defined as the date of disease recurrence, of death from any cause, or of last follow-up from the date of surgery. Typically, OS and DFS were plotted using the Kaplan–Meier method; the log-rank test was used for intergroup comparisons. Univariate and multivariate Cox regression analyses were used to judge whether selected variables were prognostic factors. A p value of 0.05 or less was considered statistically significant. For multiple comparisons, the significance level was adjusted to 0.05 / k according to the frequency of comparison (k times). All statistical analyses were completed using the IBM SPSS Statistics software application (version 25.0: IBM, Armonk, NY, U.S.A.).

RESULTS

Baseline Comparisons

Median age for the 440 study patients was 59 years, and most were men (n = 298, 67.7%). Of the 223 patients (50.7%) who had received PORT, 41 (18.4%) were classified as N2a1; 99 (44.4%), as N2a2; and 83 (37.2%), as N2b. In the non-PORT group (n = 217), 57 (26.3%) were classified as N2a1; 100 (46.1%), as N2a2; and 60 (27.6%), as N2b. Results of the chi-square test revealed that the differences in the N classifications for the PORT and non-PORT groups were statistically significant (χ^2 = 6.236, p = 0.044). Table I presents the clinical and pathologic features of patients by N stage. The baseline characteristics of patients at each N classification in the PORT and non-PORT groups were comparable, except for the POCT cycle in patients classified N2a1 (p = 0.036) and the chemotherapy regimen (p = 0.045) and visceral pleural invasion status (p = 0.009) of patients classified N2b. The Kruskal–Wallis H test revealed that the total RT dose was not significantly different in the N2 subgroups of patients who received PORT (χ^2 = 2.005, p = 0.367).

Survival Analysis

Using the log-rank test, the OS and DFS of patients from each N classification were compared for the PORT and non-PORT groups (Figure 1). Table II shows the patterns of first recurrence in the various subgroups.

For the 98 patients classified N2a1, median follow-up was 41.6 months (range: 4.4–114.6 months), and 36 patients (36.7%) had experienced recurrence. Results of the chi-square test showed that the rate of local recurrence at first recurrence (9.8% in the PORT group and 12.3% in the non-PORT group) was not significantly different (χ^2 = 0.004, p = 0.947). Of those 98 patients, 31 (31.6%) had died. The 3-year OS and DFS rates in the PORT group were 68.4% and 52.1% respectively; the equivalent rates in the non-PORT group were 76.1% and 61.7%. The log-rank test showed that the differences in OS and DFS in the two groups were not statistically significant [p = 0.304, p = 0.197, Figure 1(A,B)].

For the 199 patients classified N2a2, median follow-up was 38.2 months (range: 3.5–117.0 months), and 102 patients (51.3%) had experienced recurrence. The rate of local recurrence at first recurrence was higher in the non-PORT group (19.0%) than in the PORT group (9.1%), and results of the chi-square test showed that the difference was significant (χ^2 = 4.040, p = 0.044). Of those 199 patients, 92 (46.2%) had died. The 3-year OS and DFS rates in the PORT group were 76.2% and 52.1% respectively; the equivalent rates in the non-PORT group were 56.2% and 38.3%. The log-rank test showed that OS and DFS rates in the PORT group were significantly superior to those in the non-PORT group [p = 0.001, p = 0.014, Figure 1(C,D)].

For the 143 patients classified N2b, median follow-up was 34.3 months (range: 4.6–115.8 months), and 95 patients (66.4%) had experienced recurrence. The rate of local recurrence at first recurrence was lower in the PORT group than in the non-PORT group (7.2% vs. 18.3%), and results of the chi-square test showed a significant difference (χ^2 = 4.100, p = 0.043). Of those 143 patients, 76 (53.1%) had died. The 3-year OS and DFS rates in the PORT group were 64.1% and 28.5% respectively; in the non-PORT group, the equivalent rates were 55.3% and 24.9%. The log-rank test showed that OS was significantly superior in the PORT group compared with the non-PORT group [p = 0.025, Figure 1(E)], but the difference in DFS was not statistically significant [p = 0.134, Figure 1(F)].

The log-rank test was also used to compare the OS and DFS for patients from the PORT and non-PORT groups classified into the two N2 groups (Figure 2). For those comparisons, the significance level was adjusted to 0.017, given that 3 pairwise comparisons were performed in each group. For patients who had not received PORT [Figure 2(A,C)], OS and DFS were markedly better for patients classified N2a1 than for those classified N2a2 (p = 0.001, p < 0.001) and N2b (p < 0.001, p < 0.001). No difference in OS or DFS was observed for the patients classified N2a2 and N2b (p = 0.425, p = 0.027). For patients who had received PORT [Figure 2(B,D)], the difference in OS between the groups was not statistically significant (N2a1 vs. N2a2, p = 0.711; N2a1 vs. N2b, p = 0.354; N2a2 vs. N2b, p = 0.095). The DFS was evidently better for patients classified N2a2 than for those classified N2b (p = 0.001), but no difference was observed compared with patients classified N2a1 (p = 0.967). Furthermore, no significant difference was observed between patients classified N2a1 and those classified N2b (p = 0.021). The rates of distant metastasis at first recurrence in patients classified N2a1, N2a2, and N2b were 32.7%, 41.7%,

TABLE I Clinical and pathologic characteristics of the study patients

Characteristic	Postoperative radiation therapy by nodal stage [*n* (%)]								
	N2a1 (*n*=98)			N2a2 (*n*=199)			N2b (*n*=143)		
	Yes (*n*=41)	No (*n*=57)	*p* Value[a] (χ^2)	Yes (*n*=99)	No (*n*=100)	*p* Value[a] (χ^2)	Yes (*n*=83)	No (*n*=60)	*p* Value[a] (χ^2)
Age									
≤60 Years	20 (48.8)	26 (45.6)	0.757	71 (71.7)	63 (63.0)	0.190	49 (59.0)	30 (50.0)	0.284
>60 Years	21 (51.2)	31 (54.4)	(0.096)	28 (28.3)	37 (37.0)	(1.719)	34 (41.0)	30 (50.0)	(1.150)
ECOG PS									
0	37 (90.2)	52 (91.2)	1.0	89 (89.9)	86 (86.0)	0.398	77 (92.8)	51 (85.0)	0.134
1	4 (9.8)	5 (8.8)	(0.0)	10 (10.1)	14 (14.0)	(0.713)	6 (7.2)	9 (15.0)	(2.240)
Sex									
Men	27 (65.9)	40 (70.2)	0.650	73 (73.7)	69 (69.0)	0.460	49 (59.0)	40 (66.7)	0.353
Women	14 (34.1)	17 (29.8)	(0.206)	26 (26.3)	31 (31.0)	(0.546)	34 (41.0)	20 (33.3)	(0.863)
History of smoking									
Yes	22 (53.7)	37 (64.9)	0.262	60 (60.6)	60 (60.0)	0.930	40 (48.2)	33 (55.0)	0.422
No	19 (46.3)	20 (35.1)	(1.261)	39 (39.4)	40 (40.0)	(0.008)	43 (51.8)	27 (45.0)	(0.646)
Pathology									
Adenocarcinoma	25 (61.0)	31 (54.4)	0.516	54 (54.5)	53 (53.0)	0.827	59 (71.1)	39 (65.0)	0.439
Other	16 (39.0)	26 (45.6)	(0.423)	45 (45.5)	47 (47.0)	(0.048)	24 (28.9)	21 (35.0)	(0.598)
Tumour location									
Left upper lobe	10 (24.4)	7 (12.3)	0.519	18 (18.2)	27 (27.0)	0.117	19 (22.9)	10 (16.7)	0.640
Left lower lobe	6 (14.6)	9 (15.8)	(3.234)	20 (20.2)	17 (17.0)	(7.373)	11 (13.3)	8 (13.3)	(2.526)
Right upper lobe	16 (39.0)	26 (45.6)		28 (28.3)	15 (15.0)		29 (34.9)	19 (31.7)	
Right middle lobe	4 (9.8)	4 (7.0)		7 (7.1)	6 (6.0)		8 (9.6)	5 (8.3)	
Right lower lobe	5 (12.2)	11 (19.3)		26 (26.3)	35 (35.0)		16 (19.3)	18 (30.0)	
Tumour type									
Central	10 (24.4)	19 (33.3)	0.339	33 (33.3)	40 (40.0)	0.329	26 (31.3)	18 (30.0)	0.865
Peripheral	31 (75.6)	38 (66.7)	(0.915)	66 (66.7)	60 (60.0)	(0.952)	57 (68.7)	42 (70.0)	(0.029)
Extent of resection									
Lobectomy	41 (100)	55 (96.5)	0.508	98 (99.0)	93 (93.0)	0.073	80 (96.4)	59 (98.3)	0.855
Pneumonectomy	0 (0.0)	2 (3.5)	(Fisher)	1 (1.0)	7 (7.0)	(3.204)	3 (3.6)	1 (1.7)	(0.034)
TNM stage[b]									
IIIA (T1–T2)	33 (80.5)	44 (77.2)	0.695	83 (83.8)	75 (75.0)	0.123	65 (78.3)	49 (81.7)	0.623
IIIB (T3–T4)	8 (19.5)	13 (22.8)	0.154	16 (16.2)	25 (25.0)	(2.376)	18 (21.7)	11 (18.3)	(0.242)
Postoperative CTx cycles									
≤2	6 (14.6)	19 (33.3)	**0.036**	18 (18.2)	28 (28.0)	0.100	19 (22.9)	17 (28.3)	0.459
>2	35 (85.4)	38 (66.7)	(4.388)	81 (81.8)	72 (72.0)	(2.698)	64 (77.1)	43 (71.7)	(0.547)
CTx regimen									
Vinorelbine–cisplatin	2 (4.9)	8 (14.0)	0.213	22 (22.2)	17 (17.0)	0.068	13 (15.7)	9 (15.0)	**0.045**
Gemcitabine–cisplatin	16 (39.0)	25 (43.9)	(Fisher)	30 (30.3)	48 (48.0)	(8.721)	22 (26.5)	23 (38.3)	(9.062)
Pemetrexed–cisplatin	12 (29.3)	11 (19.3)		29 (29.3)	17 (17.0)		35 (42.2)	13 (21.7)	
Paclitaxel–cisplatin	11 (26.8)	10 (17.5)		16 (16.2)	14 (14.0)		13 (15.7)	13 (21.7)	
Other regimens	0 (0.0)	3 (5.3)		2 (2.0)	4 (4.0)		0 (0.0)	2 (3.3)	
Lymph node ratio									
≤20%	41 (100.0)	53 (93.0)	0.225	47 (47.5)	44 (44.0)	0.623	20 (24.1)	15 (25.0)	0.901
>20%	0 (0.0)	4 (7.0)	(1.475)	52 (52.5)	56 (56.0)	(0.242)	63 (75.9)	45 (75.0)	(0.015)
Bronchial involvement									
Yes	20 (48.8)	29 (50.9)	0.838	53 (53.5)	54 (54.0)	0.948	36 (43.4)	36 (60.0)	0.050
No	21 (51.2)	28 (49.1)	(0.042)	46 (46.5)	46 (46.0)	(0.004)	47 (56.6)	24 (40.0)	(3.851)
Pulmonary vascular wall invasion									
Yes	4 (9.8)	9 (15.8)	0.385	18 (18.2)	22 (22.0)	0.502	18 (21.7)	19 (31.7)	0.179
No	37 (90.2)	48 (84.2)	(0.754)	81 (81.8)	78 (78.0)	(0.452)	65 (78.3)	41 (68.3)	(1.808)

TABLE I Continued

Characteristic	Postoperative radiation therapy by nodal stage [*n* (%)]								
	N2a1 (*n*=98)			N2a2 (*n*=199)			N2b (*n*=143)		
	Yes (*n*=41)	No (*n*=57)	*p* Value[a] (χ^2)	Yes (*n*=99)	No (*n*=100)	*p* Value[a] (χ^2)	Yes (*n*=83)	No (*n*=60)	*p* Value[a] (χ^2)
Visceral pleural invasion									
Yes	22 (53.7)	24 (42.1)	0.258	49 (49.5)	46 (46.0)	0.622	43 (51.8)	44 (73.3)	**0.009**
No	19 (46.3)	33 (57.9)	(1.278)	50 (50.5)	54 (54.0)	(0.244)	40 (48.2)	16 (26.7)	(6.773)
Lymphovascular invasion									
Yes	8 (19.5)	10 (17.5)	0.804	38 (38.4)	32 (32.0)	0.346	36 (43.4)	24 (40.0)	0.687
No	33 (80.5)	47 (82.5)	(0.062)	61 (61.6)	68 (68.0)	(0.889)	47 (56.6)	36 (60.0)	(0.163)
Perineural invasion									
Yes	2 (4.9)	8 (14.0)	0.255	22 (22.2)	22 (22.0)	0.970	16 (19.3)	10 (16.7)	0.690
No	39 (95.1)	49 (86.0)	(1.297)	77 (77.8)	78 (78.0)	(0.001)	67 (80.7)	50 (83.3)	(0.160)

[a] Significant values are shown in boldface type.
[b] According to the 8th edition of the American Joint Committee on Cancer staging manual.
ECOG PS = Eastern Cooperative Oncology Group performance status; Fisher = *p* value by the Fisher exact test; CTx = chemotherapy.

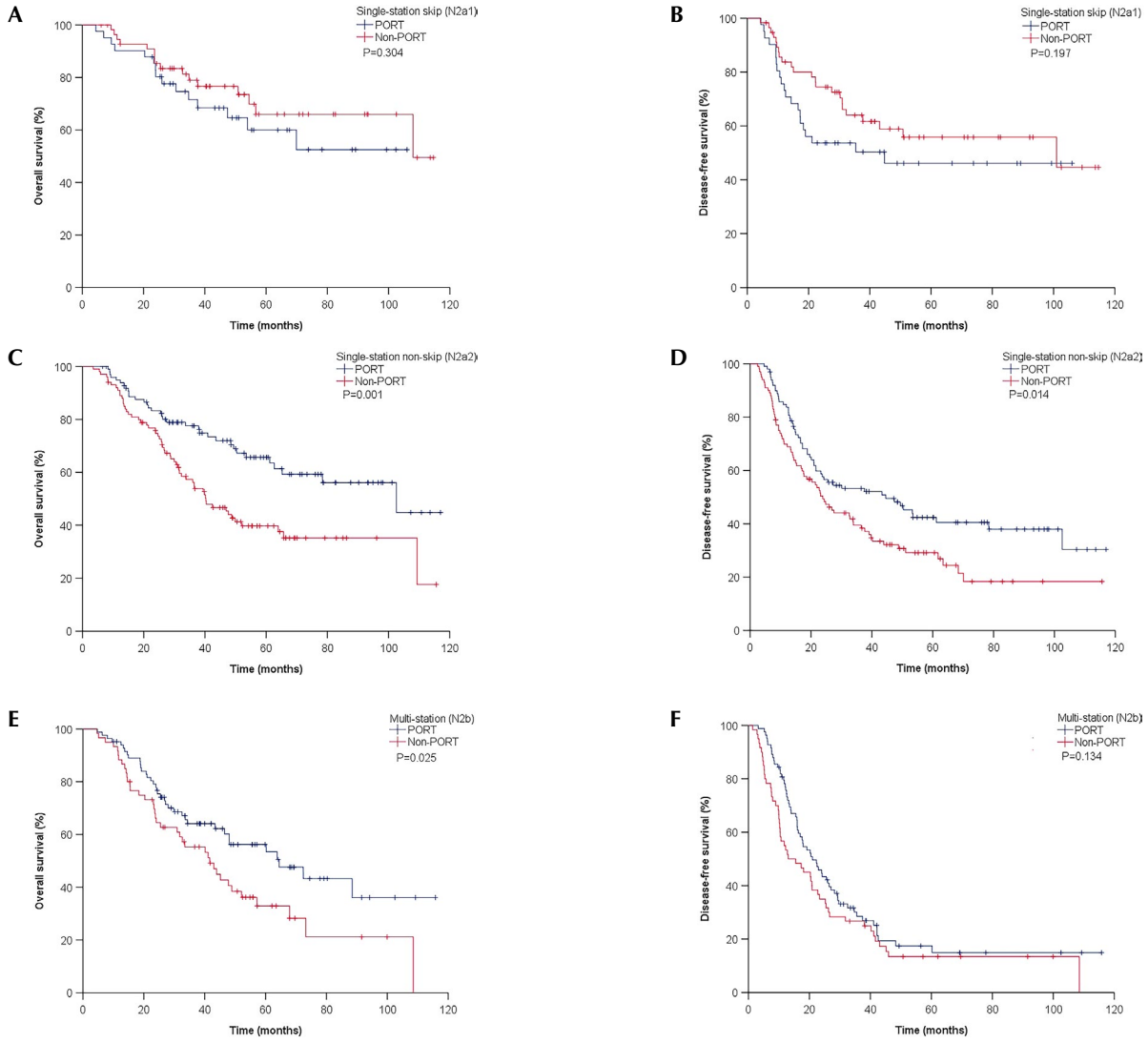

FIGURE 1 Kaplan–Meier survival curves for patients with N2a1, N2a2, and N2b non-small-cell lung cancer (NSCLC). (A) Overall survival (OS) and (B) disease-free survival (DFS) in N2a1 NSCLC. (C) OS and (D) DFS in N2a2 NSCLC. (E) OS and (F) DFS in N2b NSCLC. PORT = postoperative radiotherapy.

TABLE II First recurrence patterns in various nodal stage subgroups

Nodal status	Recurrence pattern	Postoperative RT [*n* (%)]		*p* Value[a]
		Yes	No	
N2a1	Local recurrence	4 (9.8)	7 (12.3)	0.947
	Distant metastasis	16 (39.0)	16 (28.1)	0.254
N2a2	Local recurrence	9 (9.1)	19 (19.0)	**0.044**
	Distant metastasis	41 (41.4)	42 (42.0)	0.933
N2b	Local recurrence	6 (7.2)	11 (18.3)	**0.043**
	Distant metastasis	54 (65.0)	34 (56.7)	0.309

[a] Significant values are shown in boldface type.
RT = radiation therapy.

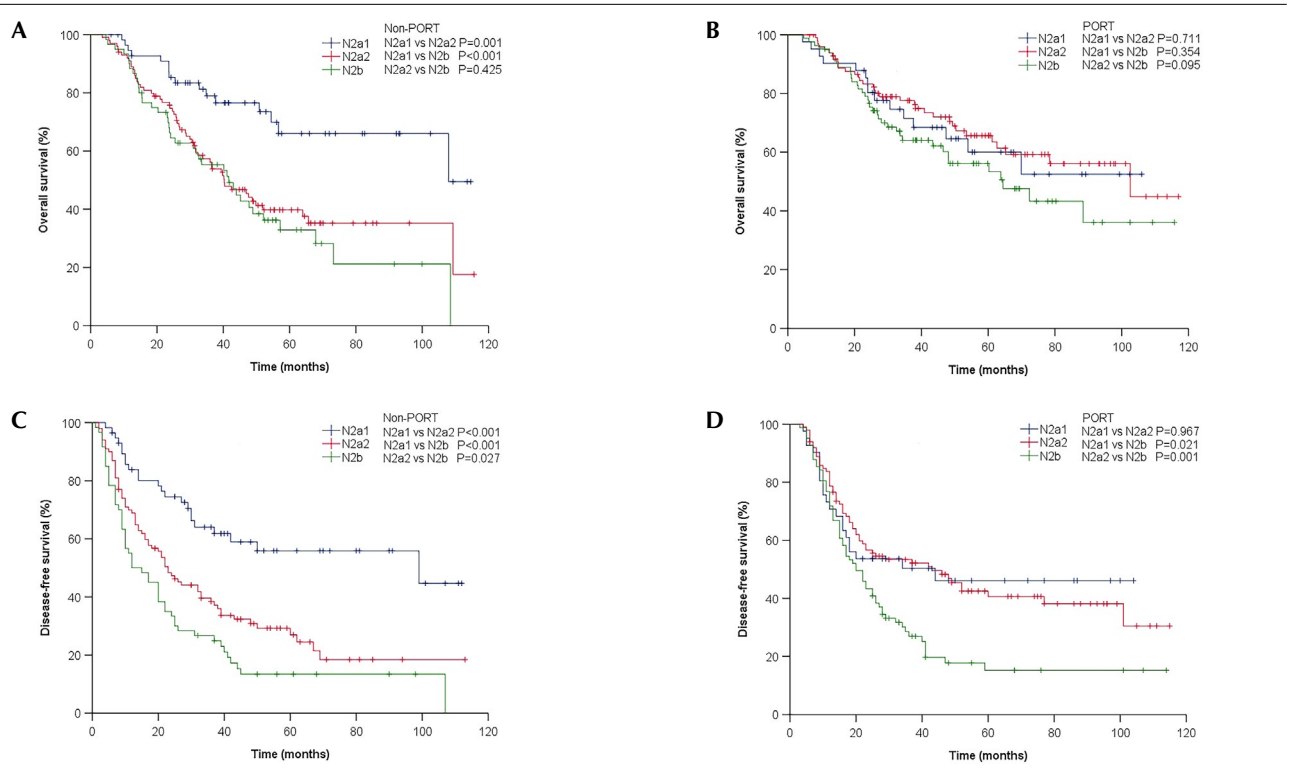

FIGURE 2 Kaplan–Meier survival curves for patients with N2a1, N2a2, and N2b non-small-cell lung cancer (NSCLC) who did or did not receive postoperative radiotherapy (PORT). (A,B) Overall survival (OS) in N2a1, N2a2, and N2b NSCLC (A) not treated with PORT and (B) treated with PORT. (C,D) Disease-free survival (DFS) in N2a1, N2a2, and N2b NSCLC (C) not treated with PORT and (D) treated with PORT.

and 61.5% respectively—a difference that was statistically significant ($\chi^2 = 22.390$, $p < 0.001$).

Univariate Analysis

In a univariate Cox regression analysis, the relationships of OS and DFS with clinicopathologic features of the patients with various N2 classifications were examined (Table III). For patients classified N2a1, age greater than 60 years ($p = 0.032$), a performance status of 1 ($p = 0.047$), non-adenocarcinoma ($p = 0.040$), pneumonectomy ($p = 0.002$), and stage IIIB disease ($p = 0.011$) were the factors markedly associated with adverse OS; in addition, pneumonectomy ($p = 0.005$) and stage IIIB disease ($p = 0.018$) were also remarkably related to poor DFS. For patients classified N2a2, not receiving PORT ($p = 0.001$), age greater than 60 years ($p = 0.024$), non-adenocarcinoma ($p = 0.014$), and LNR greater than 20% ($p < 0.001$) were the factors significantly associated with adverse OS; factors that were markedly associated with adverse DFS also included not receiving PORT ($p = 0.015$), age greater than 60 years ($p = 0.011$), LNR greater than 20% ($p = 0.002$), and visceral pleural invasion ($p = 0.041$). For patients classified N2b, the factors markedly associated with adverse OS were not receiving PORT ($p = 0.027$), history of smoking ($p = 0.009$), and 2 or fewer POCT cycles ($p = 0.001$). In those patients, no factor was significantly associated with adverse DFS.

TABLE III Univariable Cox regression analysis of overall survival (OS) and disease-free survival (DFS) by nodal stage

Characteristic	Comparator	Survival type	Nodal status								
			N2a1			N2a2			N2b		
			HR	95% CI	*p* Value[a]	HR	95% CI	*p* Value[a]	HR	95% CI	*p* Value[a]
Age	>60 Years vs. ≤60 years	OS	2.338	1.075 to 5.088	**0.032**	1.625	1.065 to 2.480	**0.024**	1.270	0.810 to 1.991	0.298
		DFS	1.657	0.895 to 3.071	0.108	1.598	1.116 to 2.290	**0.011**	0.904	0.627 to 1.304	0.590
ECOG PS	1 vs. 0	OS	2.487	1.011 to 6.117	**0.047**	0.753	0.396 to 1.432	0.387	1.327	0.699 to 2.518	0.387
		DFS	1.657	0.700 to 3.924	0.251	0.761	0.433 to 1.337	0.342	1.561	0.891 to 2.734	0.120
Sex	Women vs. men	OS	0.599	0.265 to 1.354	0.218	0.834	0.532 to 1.308	0.430	0.650	0.395 to 1.067	0.089
		DFS	1.234	0.667 to 2.282	0.503	1.063	0.730 to 1.547	0.750	0.830	0.568 to 1.213	0.337
History of smoking	No vs. yes	OS	0.577	0.270 to 1.233	0.155	1.027	0.680 to 1.551	0.899	0.539	0.338 to 0.857	**0.009**
		DFS	0.799	0.442 to 1.447	0.460	1.164	0.819 to 1.654	0.396	1.013	0.703 to 1.460	0.945
Pathology	Other vs. adenocarcinoma	OS	2.109	1.035 to 4.298	**0.040**	1.677	1.112 to 2.529	**0.014**	1.095	0.669 to 1.792	0.719
		DFS	1.315	0.724 to 2.387	0.369	1.020	0.717 to 1.450	0.913	1.000	0.669 to 1.494	0.998
Tumour type	Peripheral vs. central	OS	0.684	0.321 to 1.458	0.325	0.731	0.482 to 1.108	0.140	0.857	0.527 to 1.395	0.535
		DFS	0.909	0.467 to 1.772	0.780	1.014	0.704 to 1.460	0.940	1.082	0.723 to 1.618	0.703
Extent of resection	Pneumonectomy vs. lobectomy	OS	11.04	2.451 to 49.788	**0.002**	1.302	0.478 to 3.552	0.606	0.658	0.161 to 2.686	0.560
		DFS	8.551	1.930 to 37.892	**0.005**	0.836	0.309 to 2.262	0.724	2.151	0.789 to 5.861	0.134
TNM stage[b]	IIIB vs. IIIA	OS	2.624	1.253 to 5.496	**0.011**	1.322	0.818 to 2.136	0.254	0.923	0.524 to 1.626	0.783
		DFS	2.160	1.142 to 4.086	**0.018**	1.307	0.858 to 1.991	0.213	0.942	0.592 to 1.500	0.801
Postoperative radiation therapy	No vs. yes	OS	0.689	0.337 to 1.409	0.307	2.016	1.318 to 3.085	**0.001**	1.664	1.060 to 2.613	**0.027**
		DFS	1.214	0.903 to 1.633	0.199	1.549	1.089 to 2.203	**0.015**	1.323	0.917 to 1.909	0.135
Postoperative CTx cycles	>2 vs. ≤2	OS	0.552	0.263 to 1.159	0.116	0.810	0.504 to 1.302	0.384	0.456	0.282 to 0.736	**0.001**
		DFS	0.670	0.350 to 1.282	0.226	0.705	0.472 to 1.054	0.088	0.728	0.481 to 1.102	0.133
Lymph node ratio	>20% vs. ≤20%	OS	2.293	0.674 to 7.797	0.184	2.224	1.430 to 3.459	**<0.001**	1.398	0.794 to 2.462	0.246
		DFS	2.239	0.796 to 6.297	0.126	1.745	1.217 to 2.503	**0.002**	1.369	0.873 to 2.147	0.172
Bronchial involvement	No vs. yes	OS	0.626	0.303 to 1.292	0.205	0.909	0.602 to 1.373	0.651	0.958	0.610 to 1.503	0.851
		DFS	0.701	0.386 to 1.272	0.242	0.909	0.641 to 1.289	0.592	1.027	0.713 to 1.479	0.886
Pulmonary vascular wall invasion	No vs. yes	OS	0.952	0.332 to 2.734	0.928	1.008	0.601 to 1.689	0.976	1.043	0.627 to 1.733	0.872
		DFS	0.927	0.391 to 2.197	0.863	0.950	0.617 to 1.463	0.816	1.055	0.695 to 1.603	0.801
Visceral pleural invasion	No vs. yes	OS	1.259	0.613 to 2.587	0.531	0.881	0.585 to 1.326	0.543	1.320	0.833 to 2.091	0.237
		DFS	1.030	0.569 to 1.863	0.923	0.694	0.489 to 0.985	**0.041**	0.930	0.637 to 1.356	0.704
Lymphovascular invasion	No vs. yes	OS	0.782	0.337 to 1.816	0.567	0.893	0.584 to 1.365	0.602	0.810	0.514 to 1.277	0.365
		DFS	0.871	0.417 to 1.820	0.714	1.011	0.701 to 1.459	0.953	0.840	0.580 to 1.215	0.354
Perineural invasion	No vs. yes	OS	1.630	0.388 to 6.844	0.505	0.917	0.568 to 1.481	0.723	0.725	0.427 to 1.233	0.235
		DFS	1.124	0.402 to 3.146	0.823	1.034	0.679 to 1.575	0.877	1.122	0.698 to 1.803	0.634

[a] Significant values are shown in boldface type.
[b] According to the 8th edition of the American Joint Committee on Cancer staging manual.
HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; CTx = chemotherapy.

Multivariate Analysis

Based on the results of the univariate analysis, a multivariate Cox regression analysis was performed. Factors (apart from PORT) included in the analysis were those with a p value less than 0.1 in the univariate Cox regression (Table IV).

For patients classified N2a1, PORT (HR: 2.618; 95% CI: 1.185 to 5.785; $p = 0.017$), age greater than 60 years (HR: 3.988; 95% CI: 1.639 to 9.702; $p = 0.002$), non-adenocarcinoma (HR: 2.303; 95% CI: 1.035 to 5.126; $p = 0.041$), stage IIIB disease (HR: 2.981; 95% CI: 1.178 to 7.545; $p = 0.021$), and pneumonectomy (HR: 21.346; 95% CI: 3.356 to 135.787; $p = 0.001$) were markedly correlated with poor OS, and pneumonectomy (HR: 6.565; 95% CI: 1.332 to 32.363; $p = 0.021$) was also remarkably correlated with adverse DFS. For patients classified N2a2, the independent predictive factors significantly correlated with OS included PORT (HR: 0.481; 95% CI: 0.314 to 0.736; $p = 0.001$), non-adenocarcinoma (HR: 1.979; 95% CI: 1.304 to 3.004; $p = 0.001$), and LNR greater than 20% (HR: 2.522; 95% CI: 1.610 to 3.950; $p < 0.001$). Factors that were significantly correlated with DFS included PORT (HR: 0.685; 95% CI: 0.479 to 0.980; $p = 0.039$), age greater than 60 years (HR: 1.518; 95% CI: 1.056 to 2.183; $p = 0.024$), and LNR greater than 20% (HR: 1.635; 95% CI: 1.128 to 2.369; $p = 0.009$). For patients classified N2b, more than 2 cycles of POCT (HR: 0.521; 95% CI: 0.319 to 0.850; $p = 0.009$) was an independent prognostic factor for OS; no independent predictive factor for DFS emerged.

Treatment Toxicity Related to PORT

The evaluation of PORT-related toxicity was based on the criteria jointly published by the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer. Of the 223 patients who received PORT, 222 completed their treatment plan. Failure of 1 patient to complete the full RT plan was a result of concurrent grade 2 radiation pneumonitis and grade 2 radiation esophagitis.

The acute adverse events most commonly reported included grades 1–2 radiation esophagitis ($n = 84$, 68 at grade 1, 16 at grade 2), grades 1–2 radiation pneumonitis ($n = 22$, 16 at grade 1, 6 at grade 2), and grades 1–2 radiation skin lesions ($n = 29$, 28 at grade 1, 1 at grade 2). Grade 3 radiation pneumonitis developed in 2 patients, but no acute adverse events greater than grade 3 and no treatment-related deaths occurred.

Other systemic reactions during treatment included mainly mild fatigue ($n = 51$) and anorexia ($n = 30$). Most of those acute adverse events were relieved with symptomatic therapy. The main late adverse events were grades 1–2 radiation-induced lung fibrosis ($n = 83$, 72 at grade 1, 11 at grade 2). No other grade 2 or greater late adverse events and no treatment-related deaths occurred during follow-up.

TABLE IV Multivariable Cox regression analysis of overall survival (OS) and disease-free survival (DFS) by nodal stage

Characteristic	Survival type	Nodal stage								
		N2a1			N2a2			N2b		
		HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age >60 years	OS	3.988	1.639 to 9.702	**0.002**	1.500	0.982 to 2.292	0.061	—		
	DFS	—			1.518	1.056 to 2.183	**0.024**	—		
ECOG PS 1	OS	2.244	0.890 to 5.657	0.087	—			—		
	DFS	—			—			—		
Female sex	OS	—			—			1.316	0.583 to 2.971	0.508
	DFS	—			—			—		
Smoking history	OS	—			—			2.005	0.935 to 4.297	0.074
	DFS	—			—			—		
Non-adenocarcinoma	OS	2.303	1.035 to 5.126	**0.041**	1.979	1.304 to 3.004	**0.001**	—		
	DFS	—			—			—		
Pneumonectomy	OS	21.346	3.356 to 135.787	**0.001**	—			—		
	DFS	6.565	1.332 to 32.363	**0.021**	—			—		
TNM stage IIIB[b]	OS	2.981	1.178 to 7.545	**0.021**	—			—		
	DFS	1.904	0.971 to 3.731	0.061	—			—		
Postoperative RT	OS	2.618	1.185 to 5.785	**0.017**	0.481	0.314 to 0.736	**0.001**	0.656	0.416 to 1.033	0.069
	DFS	1.595	0.870 to 2.925	0.131	0.685	0.479 to 0.980	**0.039**	0.756	0.524 to 1.091	0.135
Postoperative CTx cycles >2	OS	—			—			0.521	0.319 to 0.850	**0.009**
	DFS	—			0.695	0.462 to 1.048	0.082	—		
Lymph node ratio >20%	OS	—			2.522	1.610 to 3.950	**<0.001**	—		
	DFS	—			1.635	1.128 to 2.369	**0.009**	—		
Visceral pleural invasion	OS	—			—			—		
	DFS	—			1.308	0.909 to 1.881	0.148	—		

[a] Significant values are shown in boldface type.
[b] According to the 8th edition of the American Joint Committee on Cancer staging manual.
HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; RT = radiation therapy; CTx = chemotherapy.

DISCUSSION

In patients with NSCLC who undergo R0 resection and receive a postoperative classification of pN2, the local recurrence rate can be as high as 20%–30% if PORT is not performed[20]. The rate of local control can be improved with PORT, but any survival benefit remains disputable[21].

Patients with NSCLC classified pN2 show great heterogeneity; PORT might therefore not be applicable for all patients. As a result, it is of crucial importance to screen patients. Yuan *et al.*[11] reported that PORT could improve survival in patients with single-station mediastinal LN metastasis, but that it was not effective in patients with multi-station metastasis. Zhang *et al.*[13] retrospectively analyzed 220 patients with pN2 NSCLC and discovered that patients with skip mediastinal LN metastasis were more likely to benefit from PORT. In fact, numerous scholars have studied mediastinal LN metastasis stations and skip metastasis in patients with pN2 NSCLC, but most have focused only on predicting prognosis. For instance, Legras *et al.*[22] retrospectively analyzed 871 patients with pN2 NSCLC in a 2-centre retrospective study, finding that patients with single-station skip metastasis had the best prognosis, followed by patients with single-station non-skip metastasis and multi-station skip metastasis. The prognosis in the latter two groups was close; patients with multi-station non-skip metastasis had the worst prognosis[22].

Based on studies such as those already mentioned, the IASLC analyzed the relationships between pathologic stage and prognosis in 31,426 patients with NSCLC, using the number of metastasis stations in combination with skip metastasis to propose a further classification of pN2 as N2a1 (single-station skip metastasis), N2a2 (singe-station non-skip metastasis), and N2b (multi-station metastasis)[14]. That proposal was not adopted into the 8th edition of the American Joint Committee on Cancer TNM staging manual because it cannot guide clinical classification[23]; however, further classification of the pathologic stage is actually of crucial importance, as manifested in the TNM staging of breast cancer[14], because the pathologic classification can not only guide prognosis, but also serve as the most important reference to formulate the postoperative treatment regimen. Based on that consideration, we attempted, in the present study, to determine which patients with pN2 NSCLC after R0 resection might benefit from PORT, referencing the IASLC's reclassification of mediastinal LN pathology.

In the present study, the application of PORT in patients with single-station skip metastasis (N2a1) did not remarkably improve the local recurrence rate, OS, or DFS (p = 0.947, p = 0.304, p = 0.197). Moreover, multivariate analysis revealed that PORT was an independent predictive factor for adverse OS (HR: 2.618; 95% CI: 1.185 to 5.785; p = 0.017). Numerous studies have proposed that the prognosis for patients with NSCLC having single-station skip mediastinal LN metastasis (N2a1) is close to that for patients with pN1 disease[14,24,25]. Thus, it could be speculated that NSCLC at the N2a1 pathologic stage might exhibit biologic behaviours similar to those at the N1 stage. So far, the ineffectiveness of PORT and its potential adverse effects for patients with pN1 NSCLC have been verified in more than one study[4,26]. It is therefore logical that patients classified N2a1 would not benefit from PORT. In addition, as suggested in Table II, the low local recurrence rate in patients classified N2a1 prevents PORT from further improving on local control, which could also be a reason that patients classified N2a1 would not benefit from PORT. With respect to the survival analysis results and our study's retrospective nature, we cannot conclude that PORT has a negative effect on the postoperative survival of patients classified N2a1. However, we at least believe that PORT is not an appropriate choice for patients classified N2a1.

For patients with single-station non-skip metastasis (N2a2), the local recurrence rate at first recurrence was higher in the non-PORT group (19.0%) than in the PORT group (9.1%), and the difference was statistically significant (p = 0.044). A log-rank test revealed that OS and DFS in the PORT group were evidently superior to those in the non-PORT group (p = 0.001, p = 0.014). Moreover, multivariate regression analysis suggested that PORT was the independent predictor of favourable OS (HR: 0.481; 95% CI: 0.314 to 0.736; p = 0.001) and DFS (HR: 0.685; 95% CI: 0.479 to 0.980; p = 0.039). In patients who had not received PORT, OS and DFS were markedly poorer in those classified N2a2 than in those classified N2a1 (p = 0.001, p < 0.001) and similar in those classified N2a2 compared with those classified N2b (p = 0.425, p = 0.027). However, for patients who had received PORT, OS and DFS were similar in those classified N2a2 and those classified N2a1, who generally have a good prognosis (p = 0.711, p = 0.967). Moreover, DFS was evidently superior in patients classified N2a2 compared with those classified N2b (p = 0.001). Those results are similar to findings in prior research that did not reclassify patients with pN2 disease[5,7].

Some previous studies have suggested that patients with NSCLC and skip mediastinal metastasis could better benefit from PORT, but those studies had enrolled few patients receiving PORT, and the balance of metastasis stations in the various groups was not taken into consideration[13]. With respect to the nature of skip metastasis, Japanese scholars have observed intraoperatively that cancer cells can drain to the subcarinal LNs directly through the subpleural pathway[27]. That study, together with an earlier study, revealed that cancer cells could metastasize to the mediastinum through two pathways: station-to-station metastasis through the intrapulmonary and hilar LNs (N1) and direct metastasis to the mediastinum by skipping N1[28]. Skip N2 adopts only the latter pathway; non-skip N2 might use both pathways at the same time. A larger number of pathways represents a higher probability of mediastinal LN recurrence and thus a greater chance to benefit from PORT[29], as verified by our results.

For patients with multi-station metastasis (N2b), the rate of local recurrence at first recurrence was lower in the PORT group than in the non-PORT group (7.2% vs. 18.3%, p = 0.043). Moreover, OS was significantly superior in the PORT group compared with the non-PORT group (p = 0.025), but the difference in DFS between the groups was not statistically significant (p = 0.134). Multivariate regression results suggested that, for OS and DFS, PORT was not an independent predictive factor (p = 0.069, p = 0.135).

Despite the log-rank test showing a significant difference in OS, multiple factors influence OS; in particular, post-recurrence treatment can have a major effect.

Unfortunately, the present study lacked accurate information about treatment after recurrence, which might, to some extent, have biased the survival analysis. We therefore believe that patients classified N2b might not benefit from PORT at the present time.

Some existing studies have verified that patients with multi-station metastasis are more likely to develop local recurrence[30], which is the foundation of the belief that patients classified N2b might benefit from PORT. However, the rates of distant metastasis at first recurrence for patients classified N2a, N2a2, and N2b in our study were 32.7%, 41.7%, and 61.5% respectively—a difference that was statistically significant ($p < 0.001$). That result is consistent with the opinion of Yuan *et al.*[11] that the local control benefit of PORT might be obscured by the high rate of distant metastasis in patients with multi-station metastasis. That observation was also consistent with our research results, given that more than 2 cycles of POCT for control of distant metastasis was the only independent predictive factor for OS (HR: 0.521; 95% CI: 0.319 to 0.850; $p = 0.009$). Consequently, we speculated that PORT might not benefit that subgroup until a better systemic treatment is developed to improve control of distant metastasis in patients classified N2b.

It cannot be ignored that the results of our study are closely related to technological improvements in RT delivery. Related research in earlier years did not achieve beneficial results because of now-outdated RT equipment and technology[4]. Currently, with the widespread use of X-ray linear accelerators and the emergence of technologies such as 3-dimensional conformal RT and intensity-modulated RT, the conformity index of the target volume, the dose distribution, and the organs at risk doses have all been improved, and radiation-related toxicity is also well controlled[6]. As a result, PORT has been validated in several studies to improve survival for patients classified pN2[5,7,8]. In the present study, PORT was implemented based on modern RT technologies (40 patients received 3-dimensional conformal RT, and 183 received intensity-modulated RT). Those patients generally showed good toleration for treatment, without serious adverse events. The results indicate that modern postoperative RT can avoid having its survival benefit obscured by therapeutic toxicity, suggesting that PORT potentially provides a benefit for patients at high risk of local recurrence and having a relatively low rate of distant metastasis.

The major limitations of our study are related to its retrospective nature. First, all enrolled patients came from the same cancer centre, and the sample size in each subgroup stratified according to mediastinal LN metastasis was small, which might lead to selection bias. Second, accurate information about treatment after recurrence was unknown for most patients, which might result in a certain degree of deviation in the survival results.

CONCLUSIONS

For patients with pN2 NSCLC who receive complete resection, PORT might be beneficial only for those with single-station non-skip metastasis (N2a2). Patients with single-station skip metastasis (N2a1) and multi-station metastasis (N2b) might not benefit from PORT at the present time. Our study highlights the value of the N2 reclassification proposed by the IASLC from the point of view of guiding postoperative treatment. Multicentric and larger prospective clinical trials are needed to further determine the patient subgroups that could benefit from PORT.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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