

## ORIGINAL ARTICLE

# Reappraisal of the role of postoperative radiation therapy in patients with pIIIa-N2 non-small cell lung cancer: A propensity score matching analysis

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## Keywords

Chemoradiotherapy; non-small cell lung cancer; prognosis; propensity score.

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## Introduction

pIIIa-N2 non-small cell lung cancer (NSCLC) is a heterogeneous disease with postoperative survival rates ranging from approximately 9–42%.<sup>1–3</sup> The International Association for the Study of Lung Cancer (IASLC) proposed a nodal zone classification whereby pN2 disease was subdivided into pN2a (single N2 zone) and pN2b (multiple N2 zones), and 14

## Abstract

**Background:** Reappraisal of the role of postoperative radiotherapy in pN2 non-small cell lung cancer (NSCLC) patients according to N1 lymph node involvement.

**Methods:** A total of 218 pIIIa-N2 NSCLC patients who underwent complete surgical resection with systematic nodal dissections were enrolled. Propensity scores were used for matching N1 involvement. Overall survival (OS) and disease-free survival (DFS) were analyzed retrospectively.

**Results:** After matching, pN2b patients without N1 involvement (pN0N2b) exhibited better prognoses than those with N1 involvement (pN1N2b) (5-year OS: 37.5% vs. 7.1%,  $P = 0.008$ ; 5-year DFS: 31.8% vs. 4.6%,  $P = 0.004$ ). Similar results were not detected in pN2a disease (5-year OS: 37.8% vs. 31.0%,  $P = 0.517$ ; 5-year DFS: 27.1% vs. 20.2%,  $P = 0.788$ ). The five-year OS of patients who received no adjuvant therapy (22 pN2a cases, 7 pN0N2b, 5 pN1N2b), adjuvant chemotherapy alone (74 pN2a cases, 11 pN0N2b, 17 pN1N2b) or chemoradiotherapy (25 pN2a cases, 7 pN0N2b, 6 pN1N2b) were compared (pN2a: 31.3%, 37.0%, and 32.0%,  $P = 0.808$ ; pN0N2b: 0.0%, 18.2%, and 71.4%,  $P = 0.108$ ; pN1N2b: 0.0%, 0.0%, and 33.3%,  $P < 0.0001$ ). The five-year DFS was also analyzed (pN2a: 31.6%, 24.0%, and 18.3%,  $P = 0.410$ ; pN0N2b: 0.0%, 11.1%, and 57.1%,  $P = 0.192$ ; pN1N2b: 0.0%, 0.0%, and 16.7%,  $P < 0.0001$ ). Multivariate analysis revealed that the novel classification based on N1 involvement and pN2a/pN2b staging was an independent prognostic factor of OS and DFS.

**Conclusion:** N1 involvement significantly impacted the prognosis of pN2b NSCLC patients. The benefit of adjuvant therapy in pN2a and pN0N2b patients requires confirmation by further study.

lymph node stations were arranged into seven lymph node zones.<sup>4,5</sup> This pN2a/pN2b classification is not currently adopted by the Union for International Cancer Control (UICC).<sup>6</sup> It is also insufficient for stratifying N2 disease by nodal zone classification; some studies have reported that pN2 patients displaying no N1 zone involvement (skip metastasis) exhibited a better prognosis than those displaying N1 involvement (continuous metastasis).<sup>7</sup> However, there has

been disagreement on the impact of N1 involvement on the prognosis of pN2 disease,<sup>7–12</sup> and previous studies have attempted to reappraise pN2 disease based on the involvement of N1 and N2 lymph nodes, with varying results.<sup>9,11–13</sup> The diversity of these results may have occurred because most of these retrospective studies failed to apply efficient methods to control confounding factors that biased the prognostic significance of N1 involvement.

Although the role of postoperative treatments, including postoperative radiation therapy (PORT), was demonstrated in our previous study<sup>14</sup> and those of others,<sup>15–17</sup> not all patients benefit from PORT.<sup>18–20</sup> Improvement in the survival of pIIIA-N2 patients who underwent PORT has been very limited.<sup>20</sup>

It is, thus, essential to select patients who respond well to PORT, and to explore individualized treatment protocols. Therefore, we attempted to balance potential confounders using a propensity score (PS) matching method, subdividing pN2a and pN2b disease based on N1 involvement, and analyzed the role of adjuvant therapy in different subgroups.

## Methods

### Eligibility and exclusion criteria

We reviewed a total of 1234 NSCLC patients who underwent complete surgical resections with systematic nodal dissections from 1 January 2008 to 31 December 2009 at Tianjin Medical University Cancer Hospital. The eligibility criteria included: no chemotherapy or radiotherapy before surgery; patients above 20 years of age; Eastern Cooperative Oncology Group performance status of 0 or 1; and written informed consent for surgical resections. Patients exhibiting one or more of the following characteristics were excluded: pN0, pN1 or pN3 disease; lymph node information unavailable; incomplete resection; history of preoperative treatment with chemotherapy or chemoradiotherapy; active double cancers; serious infection; serious cardiac, hepatic, renal or psychological diseases at the time of surgery; and intraoperative anticancer drug administration.

### Pre-operative diagnosis and treatments

Positron emission tomography-computed tomography (PET-CT) scanning, in some cases with mediastinoscopy, was the most common pre-operative diagnostic method for identifying mediastinal lymph node metastasis. All patients received pre-operative examinations to exclude distant metastasis; the examinations included PET-CT or chest multi-slice spiral CT, abdominal CT or ultrasonography examination, brain magnetic resonance imaging, and whole-body bone scan.

Major surgical resections included anatomic lobectomy, bilobectomy, pneumonectomy, and wedge resection. Adju-

vant chemotherapies included vinorelbine (25 mg/m<sup>2</sup>), paclitaxel (200 mg/m<sup>2</sup>), or gemcitabine (1250 mg/m<sup>2</sup>) and carboplatin (AUC = 5) or cisplatin (75 mg/m<sup>2</sup>) for four to six cycles. Patients receiving PORT underwent radiotherapy simulation using a CT simulator while supine and immobilised using thermoplastic resin shells. CT was performed from the mandible to the adrenal gland using a slice thickness of 5 mm. The patients displayed no gross tumor volume (GTV) because they received complete resection. The ipsilateral hilum, the ipsilateral mediastinal zone displaying lymph node metastasis, and the subcarinal zone were included in the clinical target volume (CTV). The planning target volume (PTV) was calculated as the CTV plus a 5–8 mm margin because of the presence of setup uncertainty and respiratory motion. Precise V2.03 treatment planning system software (Elekta, Sweden) was applied to calculate the three-dimensional conformed radiotherapy treatment plans. At least 95% of the PTV received the prescribed dose. The radiation dose to the PTV was 50.4Gy at 1.8Gy/fraction if the patients tolerated this dose well. Three to five beams were generally used in the treatment plans. Heterogeneity correction was applied to all of the plans for dose calculation. The dose constraints for normal tissues were as follows: to the spinal cord, <45 Gy; to the heart, V40 < 40%; and to the whole lung, V20 < 25% in patients who received lobectomy or < 10% in patients who received pneumonectomy.

### Staging and classification

The 7th edition tumor node metastasis (TMN) staging system recommended by the IASLC and the UICC was applied to re-evaluate stage.<sup>4,6,21</sup> Complete resection was defined as neither microscopic nor macroscopic residual tumor. The definition of systematic nodal dissections followed European Society of Thoracic Surgeons guidelines, which recommend that at least three mediastinal nodal stations (always including the subcarinal nodes) should be excised.<sup>22</sup> pN2 NSCLC was subdivided into pN2a (single N2 zone) and pN2b (multiple N2 zones). pN2 NSCLC was also subdivided into pN1N2 and pN0N2, respectively, according to whether N1 lymph nodes were involved or not. Then, both pN2a and pN2b diseases were subdivided based on N1 involvement. Prognoses of patients in different subclassifications were compared.

### Follow-up and statistical analysis

Patients were followed up once every three months for the first two years following surgery and every six months thereafter. Follow-up methods included telephone interviews or direct outpatient clinic consultations. Data for survival and cause of death were collected and checked by four trained staff members of our department. The end-point of

follow-up was March 2014 or the date of death. Toxicity of chemoradiotherapy was identified based on Common Terminology Criteria for Adverse Events version 4.0.<sup>23</sup>

Potential confounding factors balanced in this study included: age; gender; pathologic T stage; pathology; tumor location; surgery type; zone classification; adjuvant therapy; number of positive mediastinal lymph nodes (MLNs); number of removed MLNs; ratio of positive MLNs; number of positive lymph node stations; and tumor size. Given the propensity scores, 1:1 nearest neighbor matching was used, meaning that the number of the matched pN0N2 patients was equal to that of the matched pN1N2 patients.

Disease free survival (DFS) was calculated from the date of surgery to any recurrent disease within the ipsilateral hemithorax or mediastinum, distant metastasis or non-cancer death. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause. The Kaplan-Meier method and log-rank test were used to compare survival rates. For multivariate analysis, the forward-stepwise Cox's proportional hazard model was applied to identify potentially prognostic factors and odds ratios (OR). *P* values were derived from two-tailed tests, and values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) and R 2.8.0 statistical package (the R Core Team, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation.

## Results

### General information

Before PS matching, 218 patients with pIIIa-N2 NSCLC were pathologically confirmed. After 1:1 matching, 87 pN0N2 patients and 87 pN1N2 patients were matched. Table 1 lists the characteristics of patients before and after matching. Before matching, N1 status was associated with several confounders including zone classification, postoperative treatment, number of positive MLNs, ratio of positive MLNs, and number of positive nodal stations. After matching, 121 (69.5%) patients displayed N2a disease and 53 (30.5%) patients displayed N2b disease. Sixty-two (71.3%) pN2a patients displayed no N1 involvement (pN0N2a), 59 (67.8%) pN2a patients displayed N1 involvement (pN1N2a), 25 (28.7%) pN2b cases displayed no N1 involvement (pN0N2b) and 28 (32.2%) pN2b patients displayed N1 involvement (pN1N2b).

### Treatments

Before matching, a total of 146 (67.0%) patients were treated with lobectomy, 24 (11.0%) with bilobectomy, 31 (14.2%) with pneumonectomy, and 17 (7.8%) with wedge resection.

Adjuvant therapy was suggested to all patients with pN2 disease. Fifty-one (23.4%) patients refused adjuvant treatment until disease progression. Of the remaining patients, 128 (58.7%) were treated with adjuvant chemotherapy alone, in which 93 (42.7%) patients received four cycles of chemotherapy, 21 (9.6%) received five cycles, and 14 (6.4%) received more than six cycles of chemotherapy. Thirty-nine (17.9%) patients were treated with adjuvant chemoradiotherapy, in which 22 (10.1%) received four cycles of chemotherapy, nine (4.1%) received five cycles, and eight (3.7%) received more than six cycles of chemotherapy. After matching, there were 116 (53.2%), 18 (8.3%), 26 (11.9%), and 14 (6.4%) patients who underwent lobectomy, bilobectomy, pneumonectomy, and wedge resection respectively. Thirty-four (19.5%), 102 (58.6%), and 38 (21.8%) patients received no adjuvant therapy, adjuvant chemotherapy alone, and adjuvant chemoradiotherapy, respectively. Among those who underwent adjuvant chemotherapy alone, 76 (43.7%), 15 (8.6%), and 11 (6.3%) patients received four, five or more than six cycles of chemotherapy, respectively. Among those who underwent adjuvant chemoradiotherapy, 22 (12.6%), eight (4.6%), and eight (4.6%) patients received four, five or more than six cycles of chemotherapy, respectively.

### Survival comparison

The five-year OS before and after matching was 28.9% and 30.5%, with median OS of 30.7 and 32.6 months, respectively. The five-year DFS before and after matching was 21.5% and 16.8% with median progression-free survival of 14.3 and 14.0 months, respectively. Univariate analyses before and after matching for OS and DFS are detailed in Table 2. Before matching, the five-year OS of pN0N2a, pN1N2a, pN0N2b, and pN1N2b was 38.4%, 32.8%, 35.6%, and 10.3%, respectively; the five-year DFS was 28.8%, 22.0%, 30.4%, and 6.5%, respectively (Table 2). After matching, the five-year OS of pN0N2a, pN1N2a, pN0N2b, and pN1N2b was 37.8%, 31.0%, 37.5%, and 7.1%, respectively; the five-year DFS was 27.1%, 20.2%, 31.8%, and 4.6%, respectively (Table 2). The five-year OS of pN2a disease before and after matching was 35.7% and 34.9%, respectively, and five-year OS before and after matching was 25.5% and 24.1%, respectively. No significant differences in prognosis were detected between pN0N2a and pN1N2a diseases before or after matching (Table 2). pN0N2b patients exhibited better prognoses than those displaying pN1N2b disease before or after matching (Table 2).

Based on forward-stepwise multivariate analysis, the novel N classification, pT stage, and pathology were independent prognostic factors affecting OS (Table 3). In addition, the novel N classification and pT stage were demonstrated as prognostic factors for DFS (Table 3).

**Table 1** Characteristics of patients before and after propensity score matching

Characteristics	Before matching (218)			After matching (174)		
	pN0N2	pN1N2	P	pN0N2	pN1N2	P
Age (years)	68 (71.6%) 27 (28.4%)	92 (74.8%) 31 (25.2%)	0.594	64 (73.6%) 23 (26.4%)	66 (75.9%) 21 (24.1%)	0.727
Gender	59 (62.1%) 36 (37.9%)	77 (62.6%) 46 (37.4%)	0.940	53 (60.9%) 34 (39.1%)	52 (59.8%) 35 (40.2%)	0.877
Performance status score (ECOG)	69 (72.6%) 26 (27.4%)	88 (71.5%) 35 (28.5%)		65 (74.7%) 22 (25.3%)	63 (72.4%) 24 (27.6%)	
pT stage	32 (33.7%) 53 (55.8%) 10 (10.5%)	41 (33.3%) 71 (57.7%) 11 (8.9%)	0.915	29 (33.3%) 50 (57.5%) 8 (9.2%)	31 (35.6%) 50 (57.5%) 6 (6.9%)	0.838
Pathology	28 (29.5%) 40 (42.1%)	42 (34.1%) 38 (30.9%)	0.395	26 (29.9%) 38 (43.7%)	31 (35.6%) 28 (32.2%)	0.426
Tumor location	17 (17.9%) 35 (36.8%) 60 (63.2%)	26 (21.1%) 56 (45.5%) 67 (54.5%)	0.197	15 (17.2%) 35 (40.2%) 52 (59.8%)	16 (18.4%) 37 (42.5%) 50 (57.5%)	0.758
Zone classification	70 (73.7%) 25 (26.3%)	65 (52.8%) 58 (47.2%)	0.002	62 (71.3%) 25 (28.7%)	59 (67.8%) 28 (32.2%)	0.621
Surgery type	63 (66.3%) 7 (7.4%) 15 (15.8%)	83 (67.5%) 17 (11.8%) 16 (13.0%)	0.268	56 (64.4%) 7 (8.0%) 14 (16.1%)	60 (69.0%) 11 (12.6%) 12 (13.8%)	0.290
Adjuvant therapy	22 (23.2%) 49 (51.6%)	29 (23.6%) 79 (64.2%)	0.037	19 (21.8%) 45 (51.7%)	15 (17.2%) 57 (65.5%)	0.168
Cycles of chemotherapy	24 (25.3%) 53 (72.6%) 12 (16.4%)	15 (12.2%) 62 (66.7%) 18 (19.4%)	0.706	23 (26.4%) 49 (72.1%) 11 (16.2%)	15 (17.2%) 49 (68.1%) 12 (16.7%)	0.817
N2 status	3.19 ± 2.85 16.05 ± 10.13	4.11 ± 3.42 13.64 ± 7.34	0.000	3.30 ± 2.99 15.15 ± 9.29	3.44 ± 3.19 14.26 ± 7.91	0.246
Ratio of positive MLNs	0.23 ± 0.20 1.49 ± 0.94	0.34 ± 0.24 2.17 ± 1.45	0.000	0.25 ± 0.20 1.52 ± 0.97	0.28 ± 0.23 1.83 ± 1.30	0.086
Tumor size	4.38 ± 2.32	4.16 ± 2.03	0.683	4.31 ± 2.30	4.01 ± 1.89	0.698

Ad, adenocarcinoma; Ad + Sq, adenosquamous carcinoma; ECOG, Eastern Cooperative Oncology Group; MLNs, mediastinal lymph nodes; No, number; SMD, standardized mean differences (absolute value); Sq, squamous carcinoma.

**Table 2** Prognostic factors under univariate analysis before and after matching

Characteristic		Five-year OS				Five-year DFS			
		Before	<i>P</i>	After	<i>P</i>	Before	<i>P</i>	After	<i>P</i>
Performance status score (ECOG)	0	30.8%	0.985	32.6%	0.955	26.2%	0.394	24.8%	0.727
	1	28.1%		29.9%		19.7%		21.3%	
pT stage	pT1	39.2%	0.008	42.8%	0.002	30.1%	0.018	32.2%	0.007
	pT2	23.5%		25.3%		16.7%		17.3%	
	pT3	23.8%		14.3%		17.0%		8.7%	
Pathology	Ad	38.5%	0.017	40.4%	0.064	21.2%	0.599	20.2%	0.821
	Sq	32.0%		33.3%		25.4%		27.6%	
	Ad + Sq	7.4%		10.0%		9.5%		12.5%	
	Others	21.0%		19.1%		22.0%		20.7%	
Tumor location	Left lung	28.9%	0.999	33.8%	0.354	25.2%	0.262	28.7%	0.085
	Right lung	28.8%		28.3%		18.8%		17.1%	
Tumor size	≤3.10	38.3%	0.004	40.5%	0.010	29.5%	0.002	30.3%	0.007
	>3.10	23.3%		24.3%		16.6%		17.0%	
No. positive MLNs	≤3	36.7%	0.021	37.9%	0.002	27.1%	0.081	27.6%	0.014
	>3	24.6%		19.1%		18.5%		14.1%	
Ratio of positive MLNs	≤0.31	35.5%	0.001	35.3%	0.019	27.8%	0.001	26.8%	0.022
	>0.31	16.9%		18.4%		10.0%		10.9%	
Involved stations	Single	39.1%	<0.0001	38.5%	0.001	26.3%	0.012	24.9%	0.125
	Multiple	17.9%		19.3%		15.9%		18.1%	
Zone classification	Single(pN2a)	35.7%	<0.0001	34.6%	0.002	25.5%	0.001	23.8%	0.048
	Multiple(pN2b)	17.7%		21.2%		14.3%		18.0%	
N1 status	Negative(pN0N2)	37.6%	0.008	37.7%	0.039	29.1%	0.022	28.3%	0.117
	Positive(pN1N2)	22.0%		23.3%		15.0%		15.6%	
pN2a disease	pN0N2a	38.4%	0.579	37.8%	0.517	28.8%	0.738	27.1%	0.788
	pN1N2a	32.8%		31.0%		22.0%		20.2%	
pN2b disease	pN0N2b	35.6%	0.009	37.5%	0.008	30.4%	0.003	31.8%	0.004
	pN1N2b	10.3%		7.1%		6.5%		4.6%	
The novel classification	pN2a	35.7%	<0.0001	34.9%	<0.0001	25.5%	<0.0001	24.1%	<0.0001
	pN0N2b	35.6%		35.6%		30.4%		30.4%	
	pN1N2b	10.3%		7.1%		6.5%		4.6%	
Surgery type	Lobectomy	30.6%	0.244	32.6%	0.145	23.9%	0.025	24.8%	0.023
	Bilobectomy	20.8%		16.7%		13.5%		6.1%	
	Pneumonectomy	23.4%		28.0%		17.2%		20.0%	
	Wedge resection	35.3%		35.7%		20.2%		25.0%	
Adjuvant therapy	Without adjuvant therapy	29.0%	0.188	26.1%	0.206	33.2%	0.074	28.8%	0.679
	Chemotherapy	25.9%		28.6%		16.7%		19.0%	
	Chemoradiotherapy	38.5%		39.5%		24.7%		25.5%	
Cycles of chemotherapy	4 cycles	23.8%	0.705	5.3%	0.349	26.3%	0.737	5.9%	0.388
	5 cycles	26.7%		17.2%		30.4%		21.7%	
	≥6 cycles	30.5%		21.5%		32.9%		23.3%	

Ad, adenocarcinoma; Ad + Sq, adenosquamous carcinoma; DFS, disease free survival; ECOG, Eastern Cooperative Oncology Group; MLNs, mediastinal lymph nodes; No, number; OS, overall survival; Sq, squamous carcinoma.

### Propensity score matching analysis and postoperative radiation therapy (PORT)

Before PS matching, pN2a patients who received no adjuvant therapy (30 cases), adjuvant chemotherapy alone (79) or chemoradiotherapy (26) did not exhibit significantly different prognoses (5-year OS: 39.7%, 36.3%, and 30.8%, respectively,  $P = 0.975$ ; 5-year DFS: 38.8%, 23.8%, and 17.3%, respectively,  $P = 0.170$ ) (Fig. 1a, d). No differing prognoses of pN0N2b patients who received no adjuvant therapy (7 cases),

adjuvant chemotherapy alone (11) or chemoradiotherapy (7) were detected (5-year OS: 0.0%, 18.2%, and 71.4%, respectively,  $P = 0.108$ ; 5-year DFS: 0.0%, 11.1%, and 57.1%, respectively,  $P = 0.192$ ) (Fig. 1b, e). pN1N2b patients who received no adjuvant therapy (14 cases), adjuvant chemotherapy alone (38) or chemoradiotherapy (6) did not exhibit significantly different five-year OS (0.0%, 7.9%, and 33.3%, respectively,  $P = 0.051$ ) or DFS (0.0%, 0.0%, and 16.7%, respectively,  $P = 0.058$ ) (Fig. 1c, f). After PS matching, pN2a patients who received no adjuvant therapy (22 cases), adjuvant chemo-

**Table 3** Results of the forward-stepwise multivariate analyses of OS and DFS before and after matching

Variables for OS	OS before matching			OS after matching			Variables for DFS	DFS before matching			DFS after matching		
	HR	95% CI	P	HR	95% CI	P		HR	95% CI	P	HR	95% CI	P
The novel classification	1.50	1.26–1.79	<0.0001	1.54	1.22–1.93	<0.0001	The novel classification	1.58	1.19–2.10	0.002	1.41	1.10–1.80	0.006
pT stage	1.44	1.11–1.85	0.005	1.63	1.20–2.21	0.002	pT stage	1.49	1.17–1.90	0.001	1.51	1.14–2.02	0.005
Pathology	1.17	1.03–1.34	0.030	1.20	1.02–1.42	0.030							

CI, confidence interval; DFS, disease free survival; HR, hazard ratio; OS, overall survival.

therapy alone (74) or chemoradiotherapy (25) did not exhibit significantly different prognoses (5-year OS: 31.3%, 37.0%, and 32.0%, respectively,  $P = 0.808$ ; 5-year DFS: 31.6%, 24.0%, and 18.3%, respectively,  $P = 0.410$ ) (Fig. 2a, d). No differing prognoses of pN0N2b patients who received no adjuvant therapy (7 cases), adjuvant chemotherapy alone (11) or chemoradiotherapy (7) were detected (5-year OS: 0.0%, 18.2%, and 71.4%, respectively,  $P = 0.108$ ; 5-year DFS: 0.0%, 11.1%, and 57.1%, respectively,  $P = 0.192$ ) (Fig. 2b, e). pN1N2b patients who received no adjuvant therapy (5 cases), adjuvant chemotherapy alone (17) or chemoradiotherapy (6) exhibited significantly different five-year OS (0.0%, 0.0%, and 33.3%, respectively,  $P < 0.0001$ ) and DFS (0.0%, 0.0%, and 16.7%, respectively,  $P < 0.0001$ ) (Fig. 2c, f).

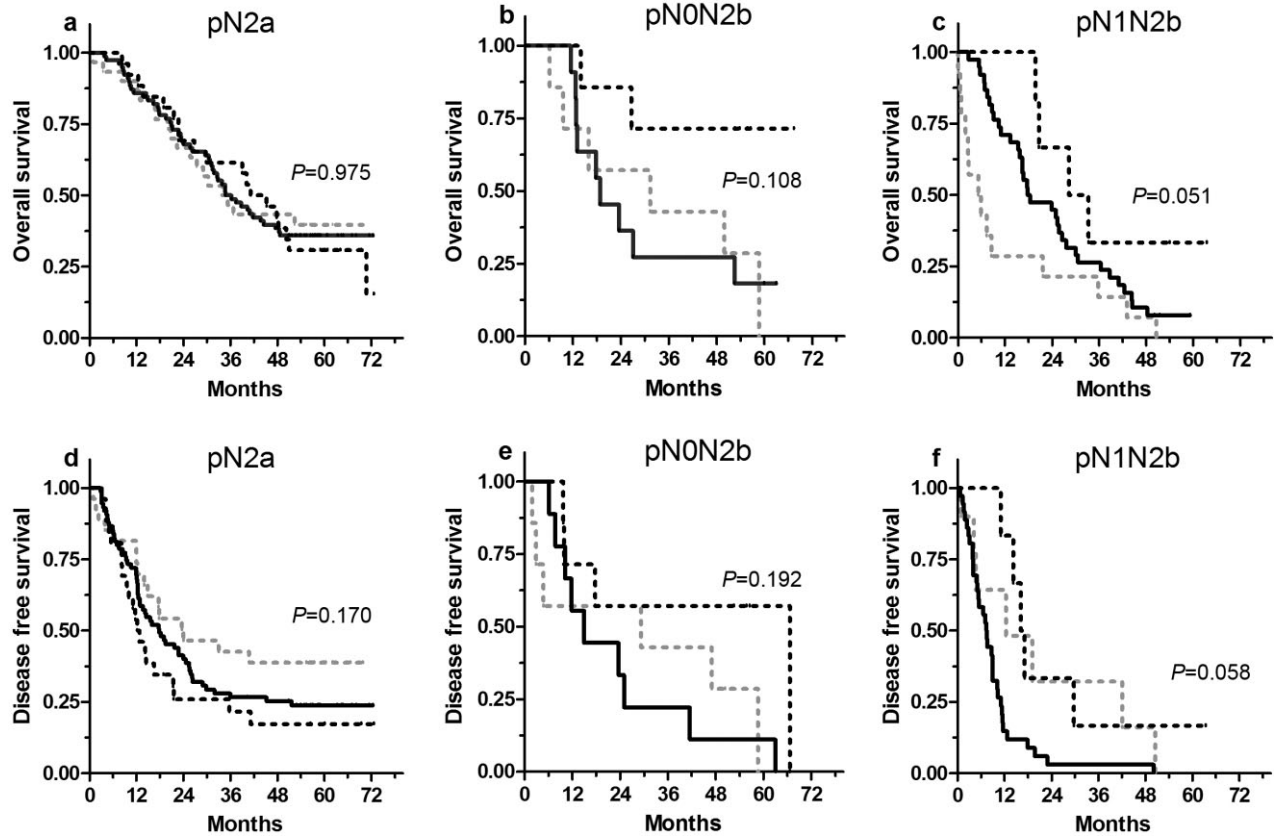
### Toxicity of PORT

Adjuvant chemoradiotherapy was well tolerated. The most common acute toxicities were grade 1 or 2 fatigue, nausea, vomiting, esophagitis, leukopenia, anemia, thrombocytopenia, and changes in liver or kidney function tests, which were resolved by routine treatments. One (4.0%) pN2a patient suffered esophageal fistula about four months after radiotherapy and was then treated with jejunostomy and total enteral nutrition. Two (8.0%) pN2a patients died of myocardial infarction about three years after radiotherapy.

### Discussion

The impact of N1 nodal zone involvement has been reported in several previous studies. Some research has revealed that pN2 NSCLC patients without N1 involvement exhibit a more favorable prognosis than those with N1 involvement.<sup>7,9,24</sup> However, the results of some other studies have reported that N1 involvement did not impact the prognosis of pN2 NSCLC patients.<sup>10,11,25,26</sup> Eligibility criteria, numbers of enrolled cases, and follow-up time were significantly diverse in these studies. Importantly, confounding factors that biased the prognostic significance of N1 involvement in pN2 NSCLC may exist in these studies. Therefore, an efficient method to control the confounders is essential. In the present study, after PS matching analysis, prognoses of patients with or without N1 involvement were compared. pN0N2 patients exhibited a significantly higher five-year OS than pN1N2 patients, although the difference of five-year DFS between pN0N2 and pN1N2 patients was not statistically significant.

The nodal zone classification of pN2 NSCLC has obtained much attention. This staging method was based only on the involvement of N2 lymph nodes.<sup>4,5</sup> However, N1 involvement is also important in pN2 NSCLC. It is necessary to reappraise pN2 NSCLC based on the combination of N1 and N2 lymph



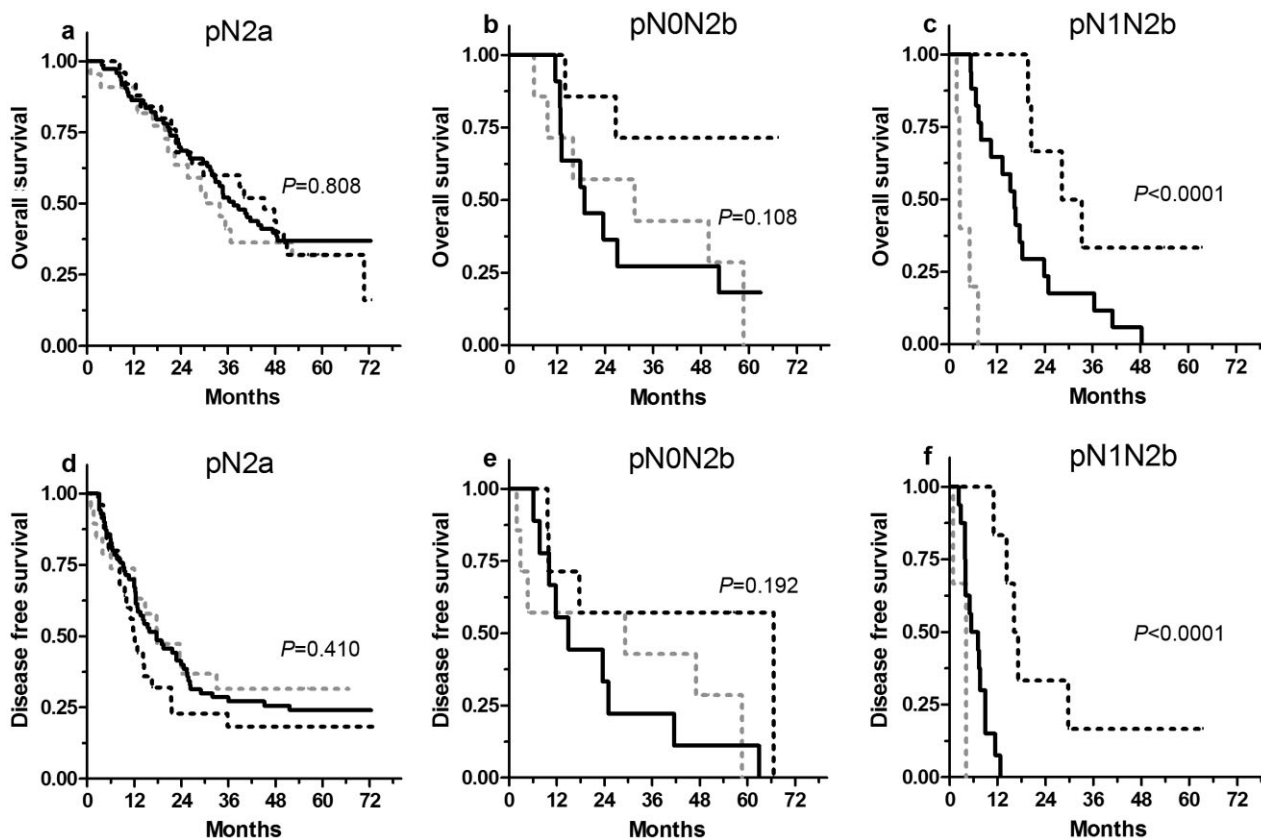
**Figure 1** Overall and disease free survival of pN2a, pN0N2b, and pN1N2b patients who received no adjuvant therapy, adjuvant chemotherapy or adjuvant chemoradiotherapy before propensity score matching. MST: median survival time; 5YSR: five-year survival rate. (a) ---, No adjuvant therapy: 30 cases; MST (months): 33.9; 5YSR: 39.7%; —, Chemotherapy: 79 cases; MST (months): 36.3; 5YSR: 36.3%; -.-, Chemoradiotherapy: 26 cases; MST (months): 41.1; 5YSR: 30.8%; (b) ---, No adjuvant therapy: 7 cases; MST (months): 31.3; 5YSR: 0.0%; —, Chemotherapy: 11 cases; MST (months): 18.7; 5YSR: 18.2%; -.-, Chemoradiotherapy: 7 cases; MST (months): 67.2; 5YSR: 71.4%; (c) ---, No adjuvant therapy: 14 cases; MST (months): 5.2; 5YSR: 0.0%; —, Chemotherapy: 38 cases; MST (months): 17.7; 5YSR: 7.9%; -.-, Chemoradiotherapy: 6 cases; MST (months): 28.3; 5YSR: 7.9%; (d) ---, No adjuvant therapy: 30 cases; MST (months): 24.0; 5YSR: 38.8%; —, Chemotherapy: 79 cases; MST (months): 17.8; 5YSR: 23.8%; -.-, Chemoradiotherapy: 26 cases; MST (months): 12.2; 5YSR: 17.3%; (e) ---, No adjuvant therapy: 7 cases; MST (months): 29.2; 5YSR: 0.0%; —, Chemotherapy: 11 cases; MST (months): 14.9; 5YSR: 11.1%; -.-, Chemoradiotherapy: 7 cases; MST (months): 66.6; 5YSR: 57.1%; (f) ---, No adjuvant therapy: 14 cases; MST (months): 12.4; 5YSR: 0.0%; —, Chemotherapy: 38 cases; MST (months): 7.4; 5YSR: 0.0%; -.-, Chemoradiotherapy: 6 cases; MST (months): 16.2; 5YSR: 16.7%.

node involvement. In our study, the significant differences in five-year OS and DFS were not observed between pN0N2a and pN1N2a patients; a result that is inconsistent with Riquet *et al.*<sup>9,12</sup> In their study, five-year OS was significantly different in single station N2 patients with and without N1 involvement (24% vs. 38.4%,  $P = 0.0005$ ).<sup>9,12</sup> In our cohort, different prognoses between different N1 status patients was only observed in pN2b patients. Because of the limited number of patients in this subgroup, our findings need to be validated in a larger cohort.

The benefit of PORT for pIIIA-N2 NSCLC remains controversial.<sup>20</sup> It is necessary to define patients who would benefit most from PORT. In this study, we attempted to analyze the impact of PORT on the prognoses of pN2a, pN0N2b, and pN1N2b NSCLC patients. Before PS matching, the prognoses

of patients in the three subgroups who received no adjuvant therapy, adjuvant chemotherapy alone or PORT were not significantly different. After PS matching, pN1N2b NSCLC patients who received PORT exhibited a significantly better prognosis than pN1N2b patients who did not undergo PORT. However, similar results were not observed in pN2a and pN0N2b NSCLC.

There are some potential weaknesses in this study. First, it was a retrospective study at a single institution and included a small number of cases in each subgroup. A prospective study with a larger number of cases is necessary to further validate our findings. Second, the radiation therapy techniques were inconsistent and modern techniques including image guidance, intensity modulated radiotherapy, and bioimaging in treatment planning or delivery were not used in most of the



**Figure 2** Overall and disease free survival of pN2a, pN0N2b, and pN1N2b patients who received no adjuvant therapy, adjuvant chemotherapy or adjuvant chemoradiotherapy after propensity score matching. MST: median survival time; 5YSR: five-year survival rate. (a) ---, No adjuvant therapy: 22 cases; MST (months): 30.3; 5YSR: 31.3%; —, Chemotherapy: 74 cases; MST (months): 37.4; 5YSR: 37.0%; -.-, Chemoradiotherapy: 25 cases; MST (months): 45.2; 5YSR: 32.0%; (b) ---, No adjuvant therapy: 7 cases; MST (months): 31.4; 5YSR: 0.0%; —, Chemotherapy: 11 cases; MST (months): 18.8; 5YSR: 18.2%; -.-, Chemoradiotherapy: 7 cases; MST (months): 53.7; 5YSR: 71.4%; (c) ---, No adjuvant therapy: 5 cases; MST (months): 2.8; 5YSR: 0.0%; —, Chemotherapy: 17 cases; MST (months): 16.4; 5YSR: 0.0%; -.-, Chemoradiotherapy: 6 cases; MST (months): 28.3; 5YSR: 33.3%; (d) ---, No adjuvant therapy: 22 cases; MST (months): 17.8; 5YSR: 31.6%; —, Chemotherapy: 74 cases; MST (months): 17.7; 5YSR: 24.0%; -.-, Chemoradiotherapy: 25 cases; MST (months): 12.2; 5YSR: 18.3%; (e) ---, No adjuvant therapy: 7 cases; MST (months): 29.2; 5YSR: 0.0%; —, Chemotherapy: 11 cases; MST (months): 14.9; 5YSR: 11.1%; -.-, Chemoradiotherapy: 7 cases; MST (months): 66.6; 5YSR: 57.1%; (f) ---, No adjuvant therapy: 5 cases; MST (months): 4.1; 5YSR: 0.0%; —, Chemotherapy: 17 cases; MST (months): 5.4; 5YSR: 0.0%; -.-, Chemoradiotherapy: 6 cases; MST (months): 16.1; 5YSR: 16.7%.

cases. Despite these limitations, our results using IASLC node classifications and N1 involvement to separate pN2 NSCLC has provided a method to enable the implementation of personalized multimodality treatments, including postoperative chemoradiotherapy.

## Conclusions

N1 status has significantly impacted the prognosis of patients with multiple nodal zones involved in pN2 NSCLC. The role of postoperative chemoradiotherapy in improving the prognosis of pN1N2b NSCLC was observed after PS matching; however the benefit of adjuvant therapy in pN2a

and pN0N2b patients requires confirmation by further study.

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## Disclosure

No authors report any conflict of interest.



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