

# Postoperative radiotherapy improves survival of patients with ypN2 non-small cell lung cancer after neoadjuvant chemotherapy followed by surgery – A propensity score matching study of the Surveillance, Epidemiology, and End Results database

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## Abstract

**Background:** For patients with ypN2 non-small cell lung cancer (NSCLC) after neoadjuvant chemotherapy followed by surgery (NCS), the role of postoperative radiotherapy (PORT) is unclear. The aim of our study was to evaluate the effect of PORT on survival of ypN2 NSCLC patients after NCS.

**Methods:** Between 2004 and 2015, patients with ypN2 NSCLC after NCS were filtrated from the Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching (PSM) was used to balance the baseline characteristics of the PORT and non-PORT groups. Kaplan–Meier method and Cox proportional hazards models were adopted to estimate overall survival (OS) and cancer-specific survival (CSS).

**Results:** A total of 257 patients who met the criteria were included in the study. After PSM, 115 patients remained in each group. The survival of patients in the PORT group was significantly better than those in the non-PORT group. Median OS was 36 months vs. 26 months, and 5-year OS rate was 40.5% vs. 21.0% ( $p = 0.002$ ). The median CSS was 38 months vs. 27 months, and the 5-year CSS rate was 43.7% vs. 22.1% ( $p < 0.001$ ). Multivariable analysis showed that PORT was an independent prognostic factor for OS (HR = 0.59, 95% CI: 0.43–0.82,  $p = 0.001$ ) and CSS (HR = 0.56, 95% CI: 0.41–0.78,  $p = 0.001$ ). Subgroup analysis showed that patients in the following subgroups could benefit from PORT: age  $\leq 70$ , diagnosed in the later period (2010–2015), white race, squamous cell carcinoma, grade III–IV, lobectomy, stage T3–4, or with positive regional nodes  $\leq 3$  or  $> 3$ .

**Conclusions:** For patients with ypN2 NSCLC after NCS, PORT significantly improves OS and CSS. These results need to be confirmed by further randomized studies.

## KEYWORDS

neoadjuvant chemotherapy, NSCLC, PORT, SEER database, ypN2

## INTRODUCTION

Neoadjuvant chemotherapy followed by surgery (NCS) is an alternative therapy pattern for patients with resectable non-

small cell lung cancer (NSCLC),<sup>1</sup> which has been demonstrated to have the same effect as adjuvant chemotherapy following surgery.<sup>2</sup> However, the locoregional recurrence (LRR) rate after NCS is still high up to 50%–60%, especially

for ypN2 patients.<sup>3,4</sup> Compared with pN2 patients, ypN2 patients might confront a higher regional tumor burden and higher risk of chemotherapy resistance. Theoretically, post-operative radiotherapy (PORT) can improve locoregional control and may further improve survival.

However, there is no prospective randomized study but a few retrospective control studies focused on the PORT for ypN2 patients. The LungART (IFCT-0503) study recently reported no survival benefit from PORT for patients with pN2 disease. However, subgroup analysis showed that PORT could significantly improve the disease-free survival (DFS) of ypN2 patients, which alludes to the fact that patients with pN2 NSCLC may benefit from PORT.<sup>5</sup> However, the other two subgroup analyses of real-world studies based on the National Cancer Database (NCDB) showed inconsistent results.<sup>6,7</sup> Thus, the role of PORT for patients with ypN2 NSCLC after NCS needs to be further evaluated.

The SEER database is a national cancer surveillance program covering approximately 26% of the United States population, another important database in addition to NCDB. Nevertheless, there has been no research on the effect of PORT on the survival of patients with ypN2 NSCLC after NCS from the SEER database. The aim of our study was to evaluate the survival benefit of PORT through the SEER database.

## METHODS

### Data collection

Our data source was SEER 18 Regs Custom Data (with additional treatment fields), November 2018 Sub (1975–2016 varying). The inclusion criteria included: (1) Patients with NSCLC diagnosed in 2004–2015, (2) patients treated with NCS, (3) patients who received lobectomy or pneumonectomy, (4) patients diagnosed with ypN2 disease after surgery. Patients who met all the following three conditions were regarded as having received NCS: (1) Met the criteria of  $\gamma$ -pathological (yp) stage which could be filtered in collaborative stage data collection system, (2) only received radiotherapy after surgery, (3) received chemotherapy. All cases were restaged according to the American Joint Committee on Cancer eighth TNM stage. Patients diagnosed in 2016 were not included because SEER did not provide the filter of yp staging after 2015. The exclusion criteria included unclear basic information, multiple primary malignant tumors, and M1 disease. Figure 1 detailed the selection process for the inclusion of patients.

The observational end-points were OS, and CSS extracted from SEER variables vital status and SEER cause-specific death classification. OS was defined as the time from diagnosis to death for any reason or last follow-up, and CSS was the interval from diagnosis to death for lung cancer or last follow-up. Demographic variables included age, period of diagnosis, race, gender, pathology, differentiation grade, surgery pattern, T stage, and the number of positive lymph nodes. All variables were categorical and cutoff values were selected according to

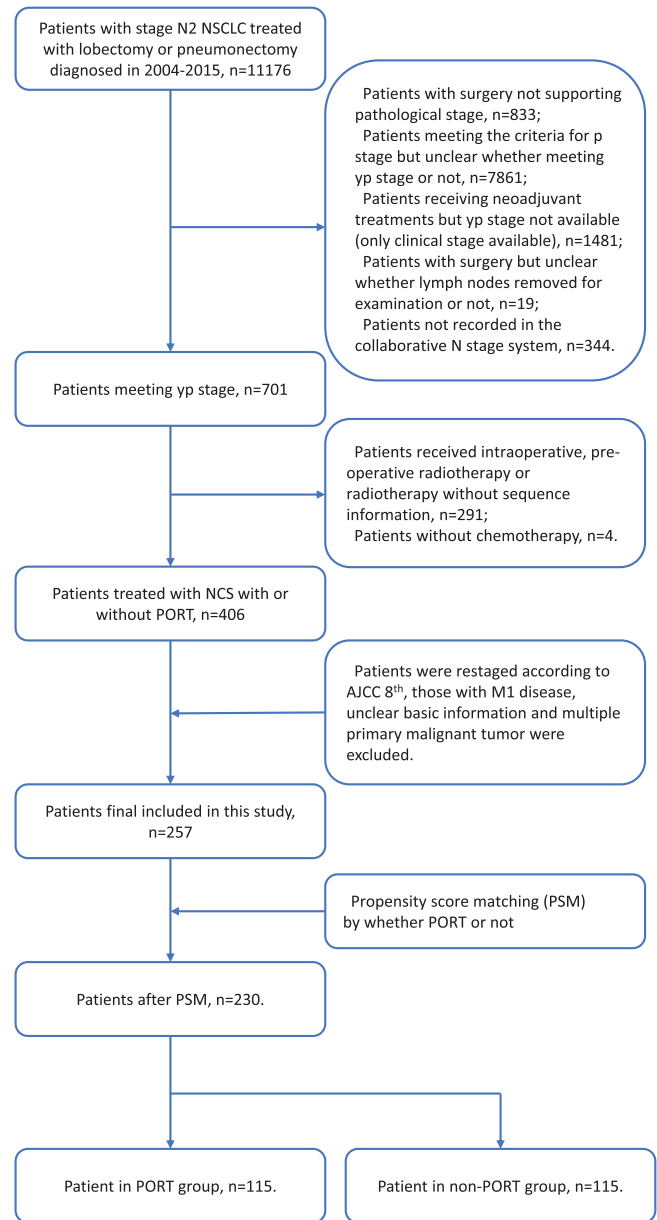


FIGURE 1 Patient selection

clinical experience and previous studies.<sup>8</sup> Patients diagnosed from 2004 to 2009 were defined as the former period, and those from 2010 to 2015 were defined as the latter period. Pathological types were classified as squamous cell carcinoma, adenocarcinoma, and other types.<sup>9</sup> Bronchioalveolar adenocarcinoma and adenocarcinoma with mixed subtypes were merged into adenocarcinoma. Patients were divided into the PORT and non-PORT groups.

### Statistical analysis

Differences of demographic variables between the PORT and non-PORT groups were analyzed by the Pearson  $\chi^2$  test. Propensity score matching (PSM) based on the greedy algorithm

(nearest neighbor matching) with caliper equal to 0.5 was used to match the baseline characteristics between the PORT and non-PORT groups. Kaplan–Meier method was used to estimate OS and CSS. Univariate and multivariate Cox proportional hazards models were adopted to estimate hazard ratios (HR) and 95% confidential interval (CI) of predictors of survival. Variables included in multivariable Cox analysis were chosen according to the results of univariable Cox analysis at a significance level of  $p < 0.1$  and clinical experience. Subgroup analysis was conducted through the univariable Cox proportional hazards model. Both original and matched data were analyzed, but only the latter was shown if they were in good consistency. Sensitivity analysis was conducted through E value for unmeasured confounders based on the results of multivariate Cox analysis, which was introduced in VanderWeele's article.<sup>10</sup> Results were considered to be statistically significant if  $p < 0.05$ . Data analysis and graph drawing were conducted through the R version 4.0.2 downloaded from <https://www.r-project.org>.

## RESULTS

### Patient characteristics

Between 2004 and 2015, 257 patients who met the criteria were included in the final analysis. The median follow-up duration was 82 months (range 4–151 months). The median

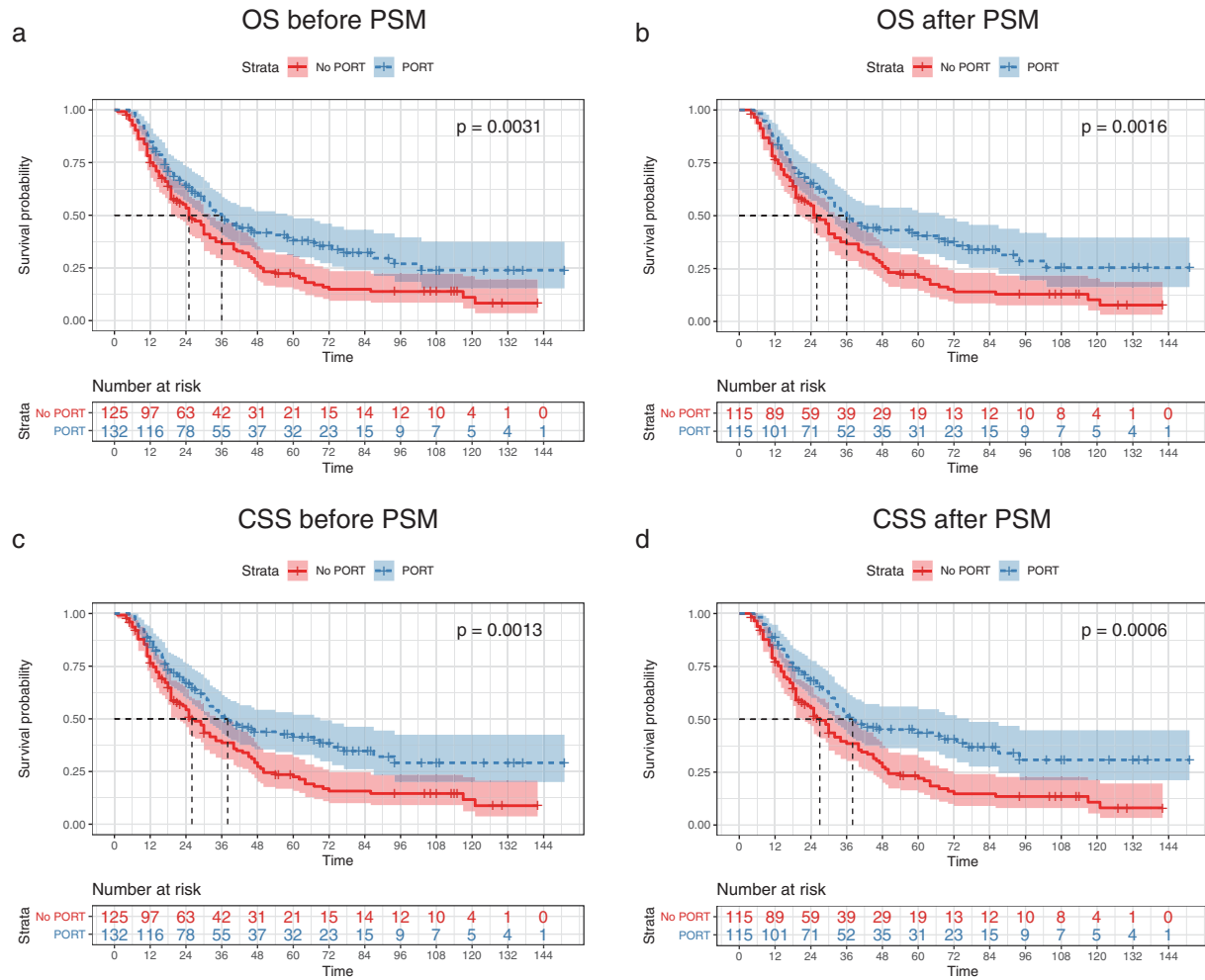
age was 63 years (range 35–89 years), and the median number of positive lymph nodes was 3 (range 0–38). Approximately half of the patients (53.7%) were stage IIIA. A total of 132 patients (51.4%) received PORT. More patients were diagnosed in the latter period or with more positive regional lymph nodes in the PORT group. After PSM, all characteristics were well balanced between the two groups, and each group had 115 patients. Table 1 shows the clinical and pathological characteristics of the PORT and non-PORT groups.

### Survival outcomes

Before PSM, the median OS was 36 months (95% CI: 30–58 months) in the PORT group and 25 months (95% CI: 19–32 months) in the non-PORT group, respectively. The 5-year OS rates were 38.2% (95% CI: 30.0%–48.5%) and 21.2% (95% CI: 14.9–30.2%), respectively ( $p = 0.003$ ). The median CSS was 38 months (95% CI: 32–69 months) in the PORT group and 26 months (95% CI: 21–34 months) in the non-PORT group. The 5-year CSS rates were 41.3% (95% CI: 32.9%–52.0%) and 22.45% (95% CI: 15.8%–31.9%), respectively ( $p = 0.001$ ) (Figure 2(a),(c)). After PSM, PORT still significantly improved survivals. The median OS of the two groups was 36 months (95% CI: 30–69 months) and 26 months (95% CI: 21–32 months), and the 5-year OS rates were 40.5% (95% CI: 31.9%–51.4%) and 21.0% (95% CI:

**TABLE 1** Baseline characteristics of patients with stage ypN2 status NSCLC before and after propensity score matching

Demographic	Subgroups	Before propensity score matching			After propensity score matching		
		No (%) of patients ( $n = 257$ )			No (%) of patients ( $n = 230$ )		
		Non-PORT	PORT	$p$ -value	Non-PORT	PORT	$p$ -value
Age	$\leq 70$	95 (76.00%)	104 (78.79%)	0.66	88 (76.52%)	91 (79.13%)	0.75
	$> 70$	30 (24.00%)	28 (21.21%)		27 (23.48%)	24 (20.87%)	
Year of diagnosis	2004–2009	72 (57.60%)	55 (41.67%)	0.01	63 (54.78%)	50 (43.48%)	0.11
	2010–2015	53 (42.40%)	77 (58.33%)		52 (45.22%)	65 (56.52%)	
Race	White	102 (81.60%)	105 (79.55%)	0.86	93 (80.87%)	92 (80.00%)	0.93
	Black	9 (7.20%)	9 (6.82%)		8 (6.96%)	7 (6.09%)	
	Other	14 (11.20%)	18 (13.64%)		14 (12.17%)	16 (13.91%)	
Gender	Male	59 (47.20%)	58 (43.94%)	0.62	55 (47.83%)	49 (42.61%)	0.51
	Female	66 (52.80%)	74 (56.06%)		60 (52.17%)	66 (57.39%)	
Histology	Squamous cell carcinoma	34 (27.20%)	28 (21.21%)	0.51	29 (25.22%)	28 (24.35%)	1.00
	Adenocarcinoma	79 (63.20%)	89 (67.42%)		74 (64.35%)	75 (65.22%)	
	Other	12 (9.60%)	15 (11.36%)		12 (10.43%)	12 (10.43%)	
Differentiation grade	I–II	48 (38.40%)	55 (41.67%)	0.61	41 (35.65%)	44 (38.26%)	0.79
	III–IV	77 (61.60%)	77 (58.33%)		74 (64.35%)	71 (61.74%)	
Surgery pattern	Lobectomy	94 (75.20%)	109 (82.58%)	0.17	90 (78.26%)	94 (81.74%)	0.62
	Pneumonectomy	31 (24.80%)	23 (17.42%)		25 (21.74%)	21 (18.26%)	
T stage	T1–2	60 (48.0%)	78 (59.1%)	0.07	60 (41.2%)	69 (60.0%)	0.23
	T3–4	65 (52.0%)	54 (40.9%)		55 (47.8%)	46 (40.0%)	
Positive regional nodes	$\leq 3$	76 (60.80%)	57 (43.18%)	0.01	66 (57.39%)	53 (46.09%)	0.11
	$> 3$	49 (39.20%)	75 (56.82%)		49 (42.61%)	62 (53.91%)	



**FIGURE 2** Survival curves according to the use of PORT before and after PSM. (a) OS curves before PSM. (b) OS curves after PSM. (c) CSS curves before PSM. (d) CSS curves after PSM

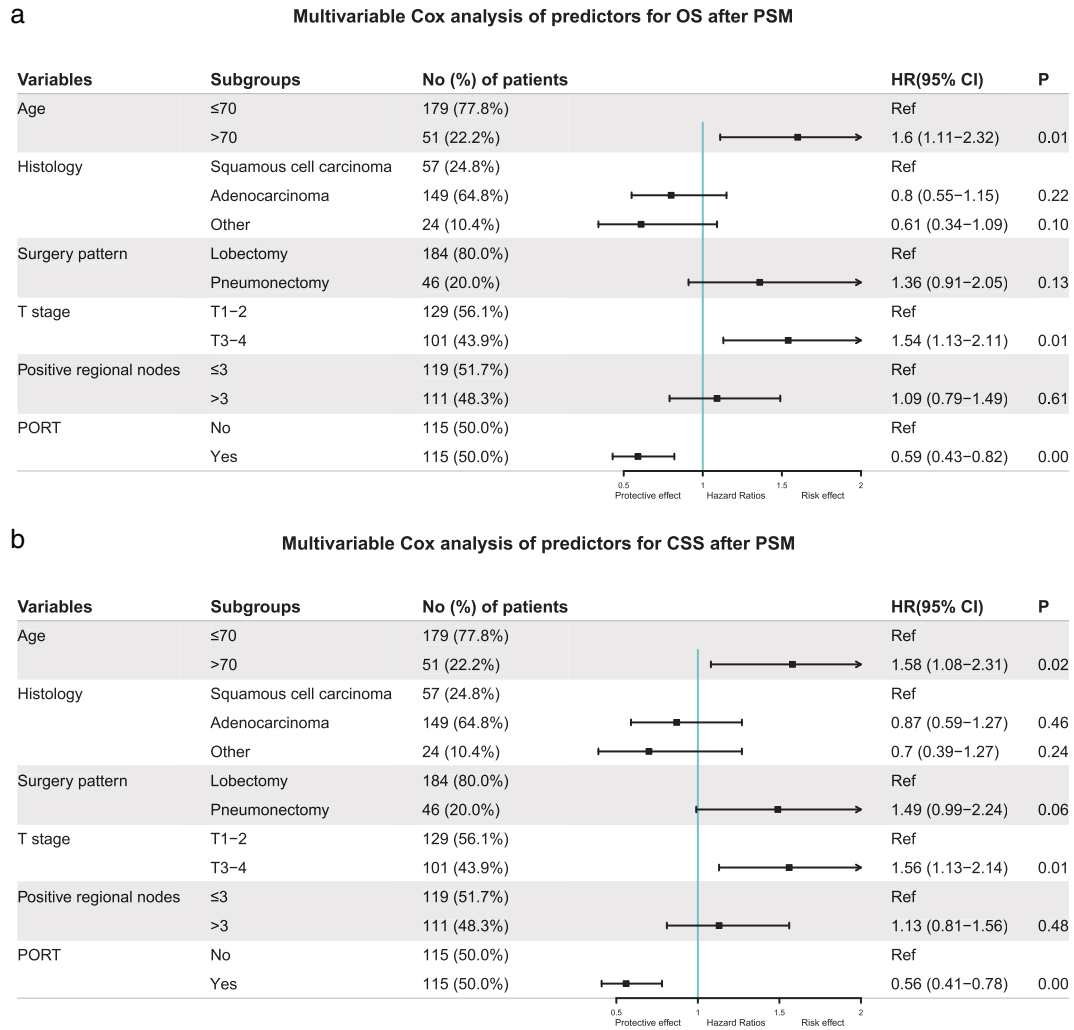
14.5%–30.5%), respectively ( $p = 0.002$ ). The median CSS was 38 months (95% CI: 32–77 months) and 27 months (95% CI: 21–36 months), and the 5-year CSS rates were 43.7% (95% CI: 34.8%–54.8%) and 22.1% (95% CI: 15.3%–31.9%), respectively ( $p < 0.001$ ) (Figure 2(b),(d)).

### Prognostic factors

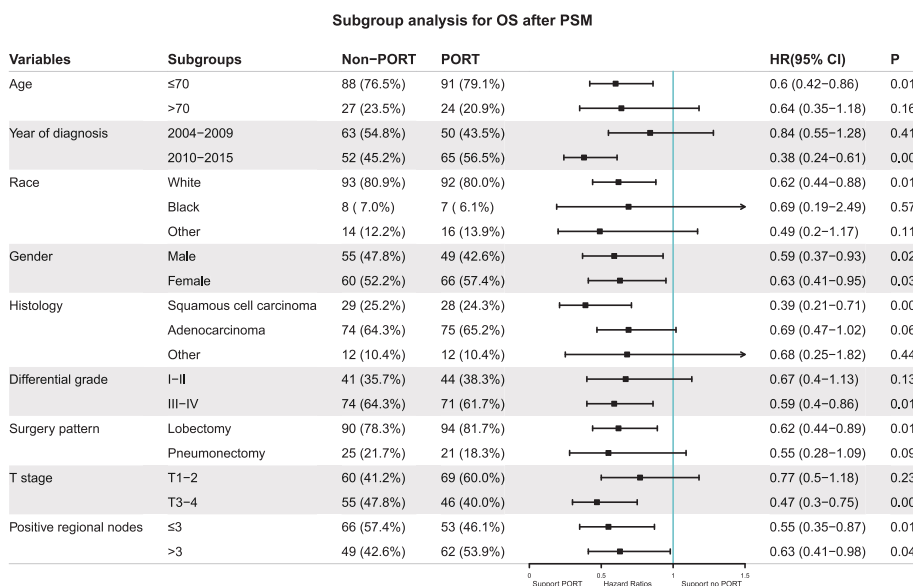
After PSM, the univariable analysis showed that PORT, age, T stage, and pneumonectomy were significantly associated with OS and CSS. Other variables did not significantly affect OS or CSS in ypN2 patients (Figures S1 and S2). In multivariable analysis, PORT was confirmed as an independent prognostic factor of OS (HR = 0.59,  $p = 0.001$ ) and CSS (HR = 0.56,  $p = 0.001$ ), as well as age (OS: HR = 1.60,  $p = 0.01$ ; CSS: HR = 1.58,  $p = 0.02$ ) and T stage (OS: HR = 1.54,  $p = 0.01$ ; CSS: HR = 1.56,  $p = 0.01$ ) (Figure 3). The results of univariable and multivariable analysis based on unmatched data were consistent with those based on matched data (Figures S3 and S6).

### Roles of PORT for the patients in different subgroup

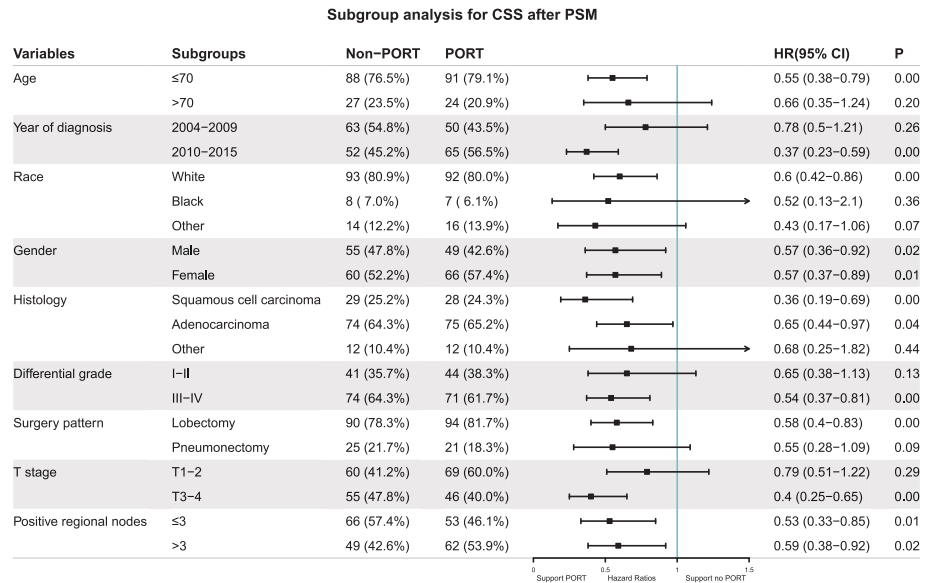
After PSM, PORT could improve OS and CSS of patients in the majority of subgroups (Figures 4 and 5), which include: age  $\leq 70$  (OS: HR = 0.60,  $p = 0.005$ ; CSS: HR = 0.55,  $p = 0.002$ ), diagnosis in latter period (OS: HR = 0.38,  $p < 0.001$ ; CSS: HR = 0.37,  $p < 0.001$ ), white (OS: HR = 0.62,  $p = 0.007$ ; CSS: HR = 0.60,  $p = 0.005$ ), male (OS: HR = 0.59,  $p = 0.025$ ; CSS: HR = 0.57,  $p = 0.02$ ) or female (OS: HR = 0.63,  $p = 0.03$ ; CSS: HR = 0.58,  $p = 0.01$ ), squamous cell carcinoma (OS: HR = 0.39,  $p = 0.002$ ; CSS: HR = 0.36,  $p = 0.002$ ), differentiation grade III–IV (OS: HR = 0.59,  $p = 0.007$ ; CSS: HR = 0.54,  $p = 0.003$ ), lobectomy (OS: HR = 0.62,  $p = 0.008$ ; CSS: HR = 0.58,  $p = 0.003$ ), T3–4 (OS: HR = 0.47,  $p < 0.001$ ; CSS: HR = 0.40,  $p < 0.001$ ), and positive regional nodes  $\leq 3$  (OS: HR = 0.56,  $p = 0.01$ ; CSS: HR = 0.53,  $p = 0.008$ ) or  $> 3$  (OS: HR = 0.64,  $p = 0.04$ ; CSS: HR = 0.59,  $p = 0.02$ ). The results of subgroup analysis based on unmatched data were consistent with those based on



**FIGURE 3** Multivariable analysis of predictors for OS and CSS after PSM. (a) Multivariable analysis of predictors for OS. (b) Multivariable analysis of predictors for CSS



**FIGURE 4** Subgroup analysis of PORT or non-PORT for OS after PSM

**FIGURE 5** Subgroup analysis of PORT or non-PORT for CSS after PSM**TABLE 2** Sensitivity analysis for OS and CSS after PSM

End points	Indicators	Point estimate	Lower 95% CI	Upper 95% CI	p-value
OS	Observed HR	0.59	0.43	0.82	0.001
	Calculated RR	0.70	0.56	0.87	-
	E value	2.22	NA	1.57	-
CSS	Observed HR	0.56	0.41	0.78	0.001
	Calculated RR	0.67	0.54	0.84	-
	E value	2.34	NA	1.66	-

matched data, except that PORT failed to significantly improve OS in male ( $p = 0.07$ ) and patients with positive regional nodes  $>3$  ( $p = 0.08$ ). (Figures S7 and S8).

## Sensitivity analysis

The results of sensitivity analysis for unmeasured confounding are shown in Table 2. The E value of 2.22 for OS meant that a set of unmeasured confounders would have to be associated with a 2.22-fold increase in the risk of death (confounder–outcome parameter,  $RR_{UD}$ ) and 2.22 times more prevalent in the PORT group than non-PORT group (exposure–confounder parameter,  $RR_{EU}$ ) to explain the observed HR for PORT. The relationships between the two parameters can be described in Figure S9. The E value for CSS was 2.34, which had similar effects as the E value for OS.

## DISCUSSION

Our study demonstrated the value of the PORT in improving OS and CSS focusing on ypN2 patients with PSM through the SEER database. The recently published

randomized phase III study (PORT-C) showed that PORT nonsignificantly improved 3-year DFS from 32.7% to 40.5% in intent-to-treat patients with pN2 NSCLC and significantly improved the DFS in per protocol patients,<sup>11</sup> which suggested that there must be a certain subgroup of patients who can benefit from PORT instead of the whole pN2 cohort. LungART (IFCT-0503) study also reported that there was no benefit from PORT for patients with N2 disease. However, the subgroup analysis showed that PORT could significantly improve the DFS of ypN2 patients, which was consistent with our study, even though the LungART study only contains 90 (18%) patients with ypN2.<sup>5</sup>

Several retrospective studies also achieved similar results with us. A retrospective study conducted by Brandt et al.<sup>12</sup> included 99 ypN2 NSCLC patients. All patients staged IIIA (cN2) preoperatively, and 69 received PORT. PORT significantly improved OS (5-year OS rate 44% vs 34%,  $p = 0.038$ ). In addition, a real-world study based on NCDB included 1541 IIIA (cN2) patients treated with NCS (sublobar resection and positive resection margin permitted) from 2004 to 2015. In the subgroup analysis of 645 patients with ypN2 disease, PORT could significantly improve OS (3-year OS rate 53.5% vs. 48.8%,  $p = 0.015$ ). Another study from NCDB, which included 1174 IIIA (cN2) patients who received neoadjuvant chemotherapy followed by lobectomy



or pneumonectomy with negative resection margin between 2006 and 2015, showed that PORT could improve OS in the subgroup analysis of 512 patients with ypN2 disease with a borderline  $p$ -value 0.072. The 5-year OS rate was 39.5% in the PORT group vs. 35.9% in the non-PORT group. Possible reasons for the borderline result might come from a short time interval for inclusion and the inclusion of negative resection margin only. Moreover, an approximately 10% relative survival benefit was observed in both studies, which indicated that the benefit of PORT existed. Furthermore, Billiet and colleagues identified 150 patients from a prospective database with III-N2 disease who received NCS. Seventy patients with ypN2 status or R1/R2 resection received three-dimensional PORT, while those with ypN0-1 and negative resection margin did not. Interestingly, patients in the PORT group, who should have a worse prognosis, achieved similar OS after modern radiotherapy techniques-based PORT as patients in the non-PORT group (5-year OS rate 32.0% vs. 38.1%,  $p = 0.44$ ).<sup>13</sup>

Compared with the aforementioned studies, the advantages of our study were as follows: holding a relative sufficient sample size, only including lobectomy and pneumonectomy to exclude patients receiving sublobectomy, utilizing the PSM method to control selection bias from known confounding factors, and utilizing sensitive analyses to estimate the effects from unknown confounding factors. The sensitivity analyses with E value showed that unmeasured confounders could not change our results unless they were risk factors of death with a RR over 2.22 for OS (2.34 for CSS) and be 2.22 times for OS (2.34 times for CSS) as distributed in the non-PORT group as it was in PORT group, which might be a relatively difficult condition to meet according to VanderWeele's article ( $\geq 2$ ).<sup>10</sup>

Even patients with the ypN2 stage also hold substantial heterogeneity and risk difference and should not be viewed uniformly. Subgroup analysis should be conducted to distinguish several groups benefitting more from PORT, which has been rarely conducted in the published studies. We performed subgroup analysis and found some interesting points: for most subgroups, both OS and CSS could benefit from PORT, especially those with age  $\leq 70$ , diagnosis in latter period, white race, male or female, squamous cell carcinoma, differentiation grades III-IV, lobectomy, stage T3-4, and positive regional nodes  $\leq 3$  or not. One of the expectable findings was that patients diagnosed in the latter period significantly benefited more from PORT compared with those in the former period. This might be due to the widespread use of more advanced radiotherapy techniques, which resulted in better protection of organs at risk (OAR) and reduced adverse effects.<sup>14</sup> Stage T3-4 disease was another subgroup that benefited from PORT. Advanced T stage meant higher local recurrence risks. In addition, we also found patients with squamous cell carcinoma benefited more from PORT compared with adenocarcinoma. A possible reason is that most squamous cell cancers are of the central-type with more advanced stages and prone to have subclinical residual tumors after surgery, which could have a relatively high LRR rate.

Our study had several limitations. Because of unmeasured confounders, the selection bias of our retrospective study might not be eliminated even using the PSM method to balance the baseline.<sup>15</sup> The data from the SEER database was observational, which might lead to inaccurate results.<sup>16</sup> Regrettably, patients receiving neoadjuvant treatments with clinical stage information only (yp stage not available) were excluded in the screening of the collaborative stage data collection system, which cut the sample size and caused selection bias in our study. In addition, the SEER database did not offer essential information such as economic status, basic performance status, comorbidities, surgical margin status, schemes and cycles of systemic therapies, or the details on PORT (technique or dose fractionation), etc. Some cases with close or positive surgical margin status were included in this study, which lead the study might overestimate the effects of PORT. Therefore, the results of this paper should be interpreted cautiously.

In summary, for patients with ypN2 NSCLC after NCS, PORT can significantly improve the OS and CSS. Prospective randomized clinical trials are needed to verify the results.

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#### CONFLICT OF INTEREST

None.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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