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ORIGINAL ARTICLE

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Effect of preoperative radiotherapy on overall survival in N2 non-small-cell lung cancer: a propensity score-matched analysis of Surveillance, Epidemiology, and End Results database

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Key question

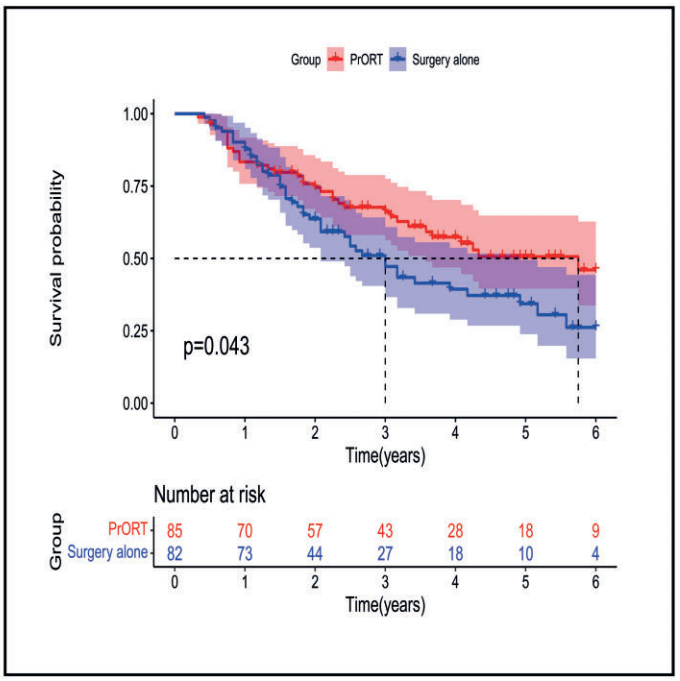
Can preoperative radiotherapy (PrORT) improve the overall survival (OS) of patients with stage N2 non-small cell lung cancer (NSCLC).

Key finding(s)

In this retrospective study of 1,390 patients with stage N2 NSCLC, subgroup analysis of the squamous cell carcinoma (SCC) group before propensity score matching (PSM) revealed that median overall survival (mOS) was significantly higher in patients who received PrORT than in those who did not receive PrORT (52 versus 27 months, P = 0.000). Notably, differences in OS were observed after PSM (P = 0.043).

Take-home message

PrORT demonstrated an OS benefit for patients with stage N2 lung SCC.



Abstract

OBJECTIVES: The aim of this study was to investigate the effect of preoperative radiotherapy (PrORT) on the overall survival (OS) of patients with stage ipsilateral mediastinal lymph node metastasis (N2) non-small-cell lung cancer.

METHODS: A total of 1390 patients with stage N2 non-small-cell lung cancer between 2010 and 2015 were identified from the Surveillance, Epidemiology, and End Results database. The efficacy of PrORT combined with surgery was compared with that of surgery alone on OS. Propensity score matching (PSM) was performed to balance the baseline characteristics of patients who received ($n = 239$) and did not receive ($n = 1151$) PrORT. We compared the OS of the 2 groups using the Kaplan–Meier method and log-rank were used to compare the OS between the 2 groups test before and after PSM and to analyse subgroups of patients with squamous cell carcinoma (SCC) and adenocarcinoma.

RESULTS: In whole group analysis before PSM, the median OS was superior in the PrORT group than in the surgery alone group (44.0 [34.4–56.6] vs 39.0 [34.5–43.5] months). There was a significant difference in OS [hazard ratio (HR): 0.819; 95% confidence interval (CI): 0.677–0.991; $P = 0.029$]. Nevertheless, no statistically significant difference was found in OS between the 2 groups after PSM (HR: 0.856; 95% CI: 0.654–1.122; $P = 0.260$). Among subgroup analysis of the SCC group before PSM revealed that patients who received PrORT had significantly higher median OS than those who did not receive PrORT (52.0 [40.0–NA] vs 27.0 [22.0–32.0] months; HR: 0.591, 95% CI: 0.442–0.792, $P = 0.000$) and the differences in OS existed after PSM ($P = 0.043$). However, no significant difference was found in OS before and after matching in the adenocarcinoma group ($P = 0.827$ and $P = 0.801$, respectively).

CONCLUSIONS: PrORT demonstrated an OS benefit for patients with stage N2 lung SCC; however, further prospective randomized clinical trials are warranted to confirm this finding.

Keywords: Non-small-cell lung cancer • Stage N2 • Preoperative radiotherapy • Overall survival • Squamous cell carcinoma • Surveillance, Epidemiology, and End Results database

ABBREVIATIONS

AC	Adenocarcinoma
CI	Confidence interval
DFS	Disease-free survival
HR	Hazard ratio
LNs	Lymph nodes
mOS	Median OS
N2	Ipsilateral mediastinal lymph node metastasis
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PORT	Postoperative adjuvant radiotherapy
PrORT	Preoperative radiotherapy
PSM	Propensity score matching
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. The American Cancer Society had estimated that new cases and deaths of lung cancer in the USA in 2018 were 2 093 876 and 1 761 007 [1], with non-small-cell lung cancer (NSCLC) cases accounting for approximately 85% of all the cases [2]. Approximately one-third of patients with NSCLC are preliminarily diagnosed with locally advanced tumours [3], and their 5-year survival rate is 13–16%. Among them, the prognosis of patients with ipsilateral mediastinal lymph node metastasis (N2) is worse, with a 3-year survival rate of only 9% after surgical resection [4, 5]. In addition, this is a group of controversial and heterogeneous diseases, and radiotherapy has always been considered an important treatment for patients with stage N2 NSCLC.

The treatment for patients with N2 NSCLC has always been the focus of clinical research. Although neoadjuvant chemotherapy plus/minus radiotherapy plus surgery or surgery plus/minus adjuvant chemotherapy plus/minus postoperative radiotherapy is recommended for patients with N2 NSCLC according to the National Comprehensive Cancer Network guidelines, the available evidence is insufficient [6]. Recently, both the Lung Adjuvant Radiotherapy Trial study and a phase III clinical study conducted by Wang *et al.* revealed that postoperative adjuvant radiotherapy (PORT) do not benefit overall survival (OS) and disease-free survival (DFS) but only improve the local control rate in patients with stage N2 NSCLC [7, 8]. Hence, the significance of PORT as one of the main interventional methods of radiotherapy was disproved. However, whether preoperative radiotherapy (PrORT), especially with sophisticated radiotherapy techniques in the new era, can benefit survival of these patients should be determined.

Therefore, we retrospectively analysed the recently updated data from the Surveillance, Epidemiology, and Results (SEER) database of patients with N2 NSCLC to explore the effects of PrORT on OS of these patients and to determine the potential advantages by subgroup analysis.

METHODS

Ethics statement

The patient information in the SEER database is publicly available and hence, our study was exempt from Ethics Review Committee approval. This study was conducted in compliance with the principles of the Declaration of Helsinki. Data of patients diagnosed with NSCLC between 2010 and 2015 were extracted from the SEER-18 Regs Custom database using SEER*Stat software (www.seer.cancer.gov). According to the time-limited and completeness of the data, we chose the data from 2010 to 2015. We included patients with NSCLC and the following parameters: pathological biopsy confirmed stage N2 NSCLC, only 1 primary malignancy, and active follow-up with complete data. In addition, we obtained permission to access the research data of the SEER program (reference number 15439-Nov2018).

Data retrieval criteria

Data of eligible patients such as age, race, sex, stage T1-4N2M0 (refer to The American Joint Committee on Cancer Seventh Edition Stage 2010), grade, laterality, histology [pathological types of squamous cell carcinoma (SCC) and adenocarcinoma (AC)], radiation sequence with surgery, radiotherapy type (all patients received external irradiation), surgery type (all patients underwent pneumonectomy and lobectomy with systematic lymphadenectomy), number of lymph nodes (LNs) examined, number of positive LNs, survival time, and vital status (refer to Supplementary Material 1 for the SEER codes) were retrieved from the database. The primary end point was OS, defined as the time from diagnosis until death from any cause.

Patient demographics

In total, 239 patients who underwent PrORT and 1151 who were treated with surgery alone without radiotherapy were included in this retrospective study. To balance the differences in covariates

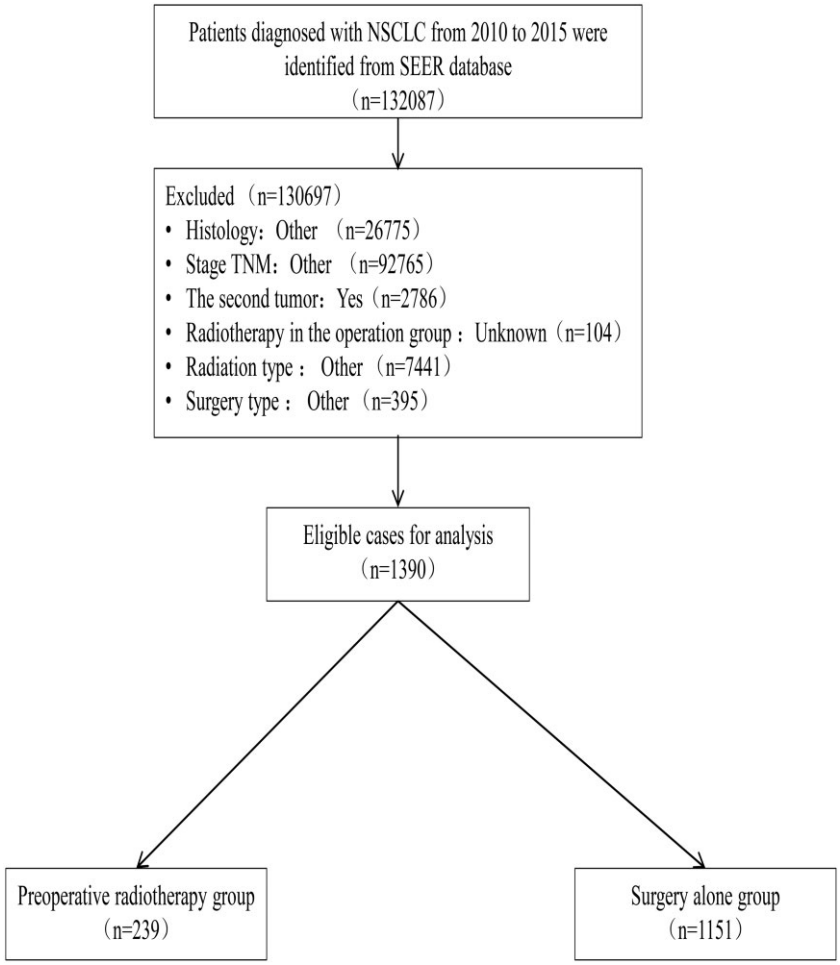


Figure 1: Data filtering flowchart.

between groups and improve the accuracy of the research results, the nearest neighbour matching method was used for propensity score matching (PSM) of the 2 groups according to the matching ratio of 1:1; the matching variables included age, race, gender, grade, laterality, stage, tumour stage, LN examined, and LN positivity. The standard mean difference was used to evaluate the balance before and after matching. Furthermore, we performed subgroup analyses based on pathological types to examine the effect of PrORT on the survival of patients with different histological types of the disease.

Statistical analyses

The SEER*Stat software (version 8.3.6.1) was used for data extraction. The log-rank test and Kaplan–Meier method were applied to assess the statistical significance of the differences between the survival curves using the SPSS software (version 22.0). The Cox proportional hazards regression model was used to estimate the effects of multiple variables on OS in the entire population before PSM and in the SCC subgroup after PSM. Logistic regression analysis was used to determine the multivariate predictors of PrORT. PSM and balance assessment were performed using the MatchIt and Stddiff packages in R software (version 3.6.2). A standard mean deviation of <0.20 indicated that the baseline characteristic balance between the 2 groups was comparable, and the difference was statistically significant ($P < 0.05$).

RESULTS

General clinical data

We enrolled 1390 patients with stage N2 NSCLC between 2010 and 2015 from the SEER database. The data filtering process is illustrated in Fig. 1. A total of 444 patients were successfully matched using PSM; thus, there were 222 patients in the PrORT group and surgery alone group each. The general clinical data of the 2 groups were comparable after PSM. The baseline characteristics of the patients before and after PSM are presented in Table 1. Multivariate Cox regression analysis revealed that age, sex, grade, stage, number of positive LNs, number of LNs examined, and PrORT were independent prognostic factors for patients with N2 stage NSCLC (Fig. 2B). In addition, multivariate logistic regression analysis revealed that PrORT was more suitable for patients with younger age, good differentiation, right lung lesion, advanced T stage, and insufficient LN dissections (Supplementary Material 2).

Survival analysis

Survival of the whole group. Before PSM, the median OS (mOS) of the study population was 40.0 months (35.9–44.2 months). The mOS was superior in the PrORT group than in

Table 1: Clinical characteristics of the patients with N2 non-small-cell lung cancer before and after propensity score matching (%)

Characteristics	Before PSM			After PSM		
	Preoperative radiotherapy group (*n* = 239)	Surgery alone group (*n* = 1151)	SMD	Preoperative radiotherapy group (*n* = 222)	Surgery alone group (*n* = 222)	SMD
Age(years), *n* (%)			0.422			0.028
≤66	161 (67.4)	540 (46.9)		145 (65.3)	142 (64.0)	
>66	78 (32.6)	611 (53.1)		77 (34.7)	80 (36.0)	
Race, *n* (%)			0.147			0.099
Black	28 (11.7)	102 (8.9)		25 (11.2)	24 (10.8)	
White	196 (82.0)	939 (81.5)		182 (82.0)	177 (79.7)	
Other	15 (6.3)	110 (9.6)		15 (6.8)	21 (9.5)	
Gender, *n* (%)			0.107			0.054
Male	129 (54.0)	560 (48.7)		118 (53.2)	112 (50.5)	
Female	110 (46.0)	591 (51.3)		104 (46.8)	110 (49.5)	
Grade, *n* (%)			0.417			0.107
I	5 (2.1)	99 (8.6)		5 (2.3)	6 (2.7)	
II	83 (34.7)	527 (45.8)		83 (37.4)	78 (35.1)	
III	149 (62.3)	515 (44.7)		133 (59.9)	135 (60.8)	
IV	2 (0.8)	9 (0.8)		1 (0.4)	3 (1.4)	
Laterality, *n* (%)			0.268			0.009
Left	81 (33.9)	540 (46.9)		81 (36.5)	82 (36.9)	
Right	158 (66.1)	611 (53.1)		141 (63.5)	140 (63.0)	
Histology, *n* (%)			0.292			0.028
SCC	97 (40.6)	310 (26.9)		85 (38.3)	82 (36.9)	
AC	142 (59.4)	841 (73.1)		137 (61.7)	140 (63.1)	
Stage, *n* (%)			0.187			0.014
IIIA	210 (87.9)	1074 (93.3)		196 (88.3)	195 (87.8)	
IIIB	29 (12.1)	77 (6.7)		26 (11.7)	27 (12.2)	
Tumour stage, *n* (%)			0.333			0.063
T1	41 (17.2)	276 (24.0)		40 (18.0)	45 (20.3)	
T2	104 (43.5)	594 (51.6)		104 (46.8)	101 (45.5)	
T3	65 (27.2)	204 (17.7)		52 (23.4)	49 (22.1)	
T4	29 (12.1)	77 (6.7)		26 (11.7)	27 (12.1)	
LN examined, *n* (%)			0.234			0.018
0–9	111 (46.4)	403 (35.0)		98 (44.1)	96 (43.2)	
≥10	128 (53.6)	748 (65.0)		124 (55.8)	126 (56.8)	
LN positivity, *n* (%)			0.035			0.011
0–5	185 (77.4)	874 (75.9)		172 (77.5)	173 (77.9)	
≥6	54 (22.6)	277 (24.1)		50 (22.5)	49 (22.1)	

AC: adenocarcinoma; LN: lymph node; PSM: propensity score matching; SCC: squamous cell carcinoma; SMD: standard mean difference.

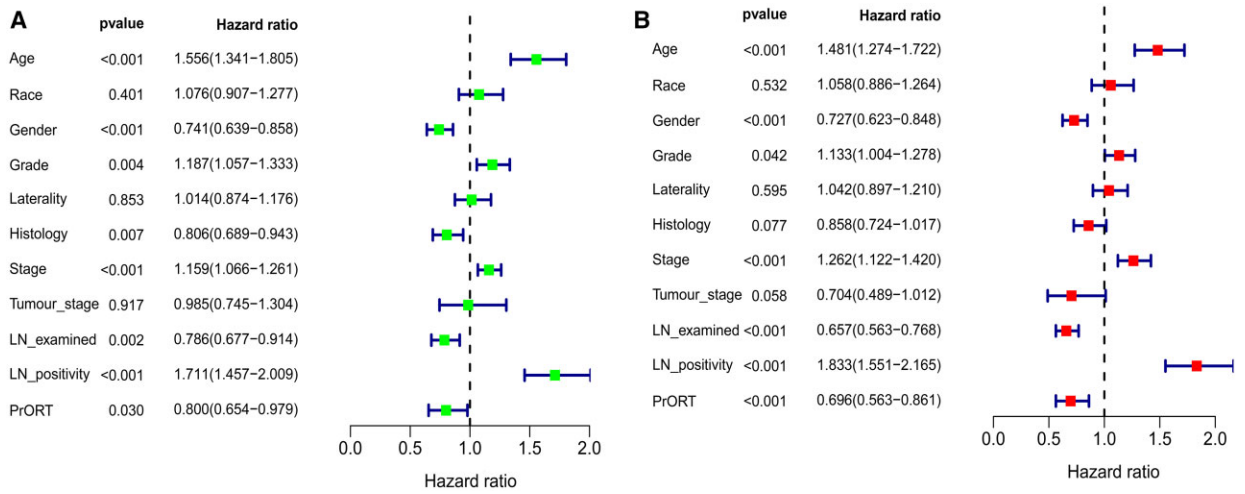


Figure 2: Results of univariate and multivariate Cox regression of prognostic factors for overall survival in patients with N2 non-small-cell lung cancer. (**A**) Univariate analysis. (**B**) Multivariate analysis.

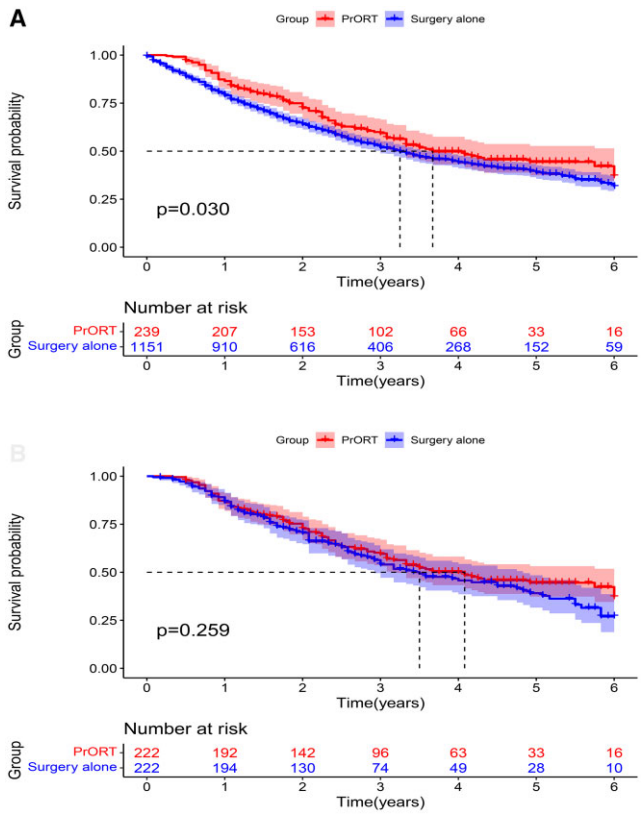


Figure 3: Overall survival curve of patients with N2 non-small-cell lung cancer. (**A**) Before propensity score matching. (**B**) After propensity score matching.

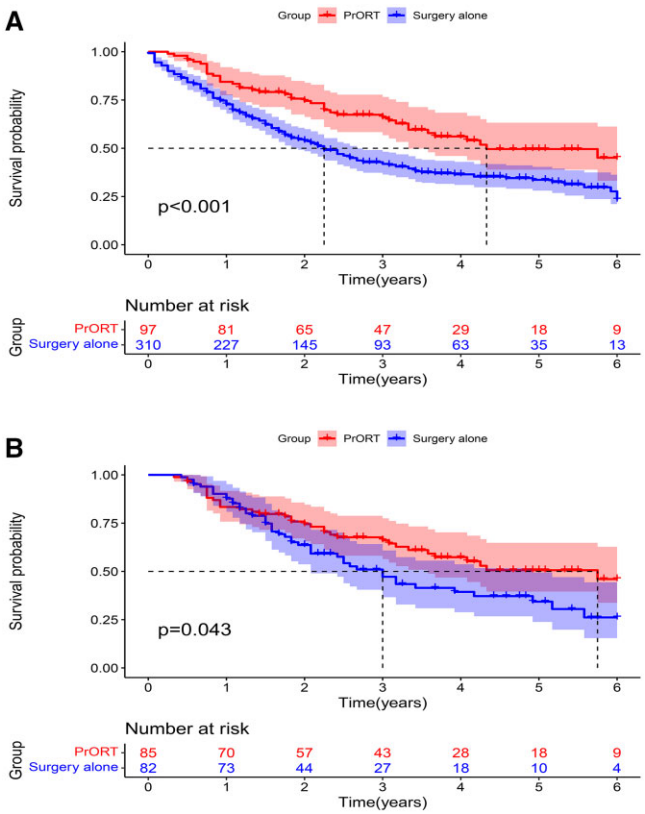


Figure 4: Overall survival curve of the squamous cell carcinoma group of patients with N2 non-small-cell lung cancer. (**A**) Before propensity score matching. (**B**) After propensity score matching.

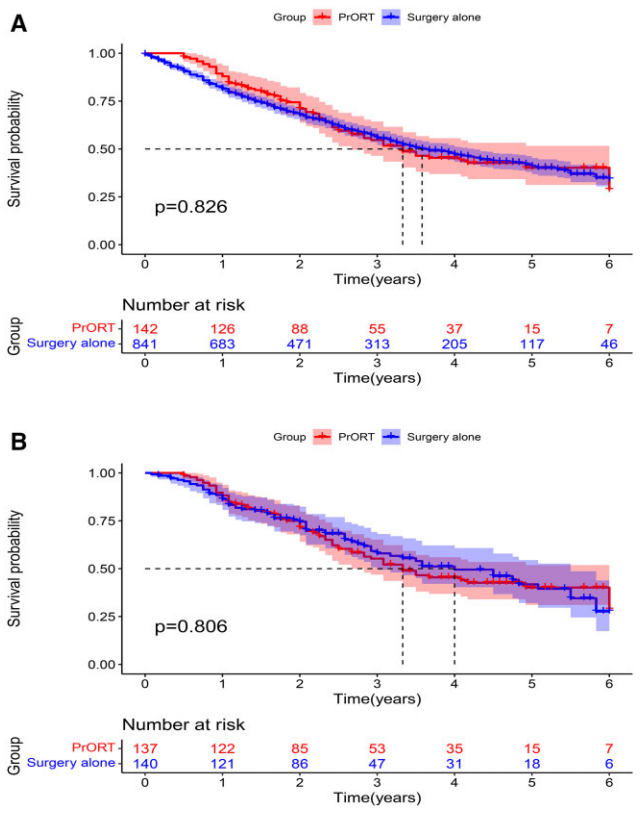


Figure 5: Overall survival curve of the adenocarcinoma group of patients with N2 non-small-cell lung cancer. (**A**) Before propensity score matching. (**B**) After propensity score matching.

the surgery alone group 44.0 (31.4–56.6) vs 39.0 (34.5–43.5) months. A significant difference in OS was found between the 2 groups [hazard ratio (HR): 0.819; 95% confidence interval (CI): 0.677–0.991; $P = 0.029$] (Fig. 3A). After PSM, the mOS was 43.0 (34.9–51.1) months. The PrORT and surgery alone group no-PrORT groups were 49.0 (35.7–62.3) and 42.0 (32.1–51.9) months, respectively. However, no statistically significant difference was found in OS between the 2 groups (HR: 0.856; 95% CI: 0.654–1.122; $P = 0.260$) (Fig. 3B).

Subgroup survival. Subgroup analysis revealed that the mOS was significantly higher in the SCC subgroup patients who received PrORT than in those who did not receive PrORT both before PSM (52.0 [40.0–NA] vs 27.0 [22.0–32.0] months; HR: 0.591, 95% CI: 0.442–0.792, $P = 0.000$) (Fig. 4A) and after PSM (69.0 [43.3–NA] and 36.0 [25.0–59.0] months; HR: 0.635, 95% CI: 0.409–0.986, $P = 0.043$) (Fig. 4B). More importantly, multivariate Cox regression analysis revealed that PrORT can benefit the SCC group (Supplementary Material 3). Nevertheless, no significant difference was found in survival analysis before and after PSM in the AC group ($P = 0.827$ and $P = 0.801$, respectively) (Fig. 5A and B). The detailed characteristics of the subgroups are presented in Tables 2 and 3.

DISCUSSION

The National Comprehensive Cancer Network guidelines recommend preoperative neoadjuvant chemoradiotherapy, simple surgical treatment and postoperative adjuvant chemoradiotherapy

Table 2: Clinical characteristics of the squamous cell carcinoma group patients before and after matching of propensity score (%)

Characteristics	Before PSM			After PSM		
	Preoperative radiotherapy group (n = 97)	Surgery alone group (n = 310)	SMD	Preoperative radiotherapy group (n = 85)	Surgery alone group (n = 82)	SMD
Age(years), n (%)			0.422			0.103
≤66	64 (66.0)	141 (45.5)		53 (62.4)	47 (57.3)	
>66	33 (34.0)	169 (54.5)		32 (37.6)	35 (42.7)	
Race, n (%)			0.134			0.172
Black	12 (12.4)	31 (10.0)		10 (11.8)	7 (8.5)	
White	80 (82.5)	254 (81.9)		70 (82.3)	67 (81.7)	
Others	5 (5.1)	25 (8.1)		5 (5.9)	8 (9.8)	
Gender, n (%)			0.081			0.128
Male	69 (71.1)	209 (67.4)		61 (71.8)	54 (65.9)	
Female	28 (28.9)	101 (32.6)		24 (28.2)	28 (34.1)	
Grade, n (%)			0.301			0.401
I	0 (0.0)	8 (2.6)		0 (0.0)	2 (2.4)	
II	37 (38.1)	133 (42.9)		37 (43.5)	25 (30.5)	
III	60 (61.9)	166 (53.5)		48 (56.5)	53 (64.6)	
IV	0 (0.0)	3 (1.0)		0 (0.0)	2 (2.4)	
Laterality, n (%)			0.343			0.153
Left	35 (36.1)	164 (52.9)		35 (41.2)	40 (48.8)	
Right	62 (63.9)	146 (47.1)		50 (58.8)	42 (51.2)	
Stage, n (%)			0.146			0.015
IIIA	83 (85.6)	280 (90.3)		73 (85.9)	70 (85.4)	
IIIB	14 (14.4)	30 (9.7)		12 (14.1)	12 (14.6)	
Tumour stage, n (%)			0.360			0.262
T1	6 (6.2)	47 (15.2)		5 (5.9)	11 (13.4)	
T2	44 (45.4)	155 (50.0)		44 (51.8)	38 (46.3)	
T3	33 (34.0)	78 (25.2)		24 (28.2)	21 (25.6)	
T4	14 (14.4)	30 (9.7)		12 (14.1)	12 (14.6)	
LN examined, n (%)			0.264			0.096
0–9	43 (44.3)	98 (31.6)		34 (40.0)	29 (35.4)	
≥10	54 (55.7)	212 (68.4)		51 (60.0)	53 (64.6)	
LN positivity, n (%)			0.045			0.017
0–5	79 (81.4)	247 (79.7)		71 (83.5)	69 (84.1)	
≥6	18 (18.6)	63 (20.3)		14 (16.5)	13 (15.9)	

LN: lymph node; PSM: propensity score matching; SMD: standard mean difference.

for patients with N2 NSCLC [6]. However, the optimal treatment method remains to be investigated because of the prominent heterogeneity of these diseases [9]. Currently, due to the development of emerging radiotherapy techniques, the adverse effects of local radiotherapy are significantly reduced, and the role of radiotherapy in NSCLC is becoming increasingly important. However, whether interventional radiotherapy and the timing of interventional radiotherapy for patients with stage N2 NSCLC undergoing surgery has gradually become the focus of attention. PORT is widely used for the treatment of patients with stage IIIA-N2 NSCLC worldwide and is thought to prolong survival [2, 10, 11]. However, previous 2 important studies have denied the significance of PORT in N2 NSCLC [7, 8]. Thus, PORT was not included in our study. Instead, we focused mainly on PrORT.

Preoperative neoadjuvant chemotherapy for patients with stage IIIA-N2 NSCLC is widely applied in Europe and North America [12]. Roth *et al.* prospectively analysed patients with resected stage IIIA NSCLC in 1994 and found that the mOS was significantly longer in the neoadjuvant chemotherapy group than in the surgery alone group (64 vs 11 months, $P = 0.008$) [13]. Another prospective randomized controlled study analysed 60 patients with stage IIIA NSCLC, of whom 73% were patients with stage N2 NSCLC. The combined results revealed that the mOS, median progression-free survival, 3-year OS (from 5% to 20%) and 5-year OS improved in the neoadjuvant chemotherapy group compared with the surgery alone group [14]. These studies initially established the vital role of neoadjuvant chemotherapy in locally advanced NSCLC treatment. Neoadjuvant radiotherapy combined with chemotherapy is considered to decrease the tumour stage, reduce the scope of surgery and improve the treatment completion rate and, thereby, increase the local control rate or improve OS and reduce the toxicity associated with the treatment [11]. In a randomized clinical trial by the West Japan Oncology Group 9903, patients with stage IIIA-N2 NSCLC who received neoadjuvant chemotherapy and radiotherapy were compared with those who only received neoadjuvant chemotherapy, the tumour stage was reduced by 40% and 21%, respectively, better local control was achieved, and there were no obvious adverse events [4]. A prospective trial of Radiation Therapy Oncology Group 0299 showed that surgical resection can be safely performed after simultaneous neoadjuvant chemotherapy and full-dose radiotherapy (61.2 Gy), which improves mediastinal LN dissection in patients with stage N2/N3 NSCLC [15, 16]. The results of the IFCT-0101 study revealed that induction radiotherapy and chemotherapy are more effective with DFS benefits than induction chemotherapy for patients with IIIA-N2 NSCLC [17]. Conversely, a large phase III randomized trial published by Pless *et al.* suggested that neoadjuvant chemoradiotherapy did not significantly improve OS compared with neoadjuvant chemotherapy in patients with stage IIIA-N2 NSCLC

Table 3: Clinical characteristics of the adenocarcinoma group patients before and after matching of propensity score (%)

Characteristics	Before PSM			After PSM		
	Preoperative radiotherapy group (*n* = 142)	Surgery alone group (*n* = 841)	SMD	Preoperative radiotherapy group (*n* = 137)	Surgery alone group (*n* = 140)	SMD
Age (years), *n* (%)			0.432			0.015
≤66	97 (68.3)	399 (47.4)		92 (67.2)	95 (67.9)	
>66	45 (31.7)	442 (52.6)		45 (32.8)	45 (32.1)	
Race, *n* (%)			0.138			0.085
Black	16 (11.3)	71 (8.4)		15 (10.9)	17 (12.1)	
White	116 (81.7)	685 (81.5)		112 (81.8)	110 (78.6)	
Others	10 (7.0)	85 (10.1)		10 (7.3)	13 (9.3)	
Gender, *n* (%)			0.010			0.004
Male	60 (42.3)	351 (41.7)		57 (41.6)	58 (41.4)	
Female	82 (57.7)	490 (58.3)		80 (58.4)	82 (58.6)	
Grade, *n* (%)			0.479			0.095
I	5 (3.5)	91 (10.8)		5 (3.6)	4 (2.9)	
II	46 (32.4)	394 (46.8)		46 (33.6)	53 (37.9)	
III	89 (62.7)	350 (41.6)		85 (62.0)	82 (58.6)	
IV	2 (1.4)	6 (0.7)		1 (0.7)	1 (0.7)	
Laterality, *n* (%)			0.255			0.077
Left	46 (32.4)	376 (44.7))		46 (33.6)	42 (30.0)	
Right	96 (67.6)	465 (55.3)		91 (66.4)	98 (70.0)	
Stage, *n* (%)			0.183			0.016
IIIA	127 (89.4)	794 (94.4)		123 (89.8)	125 (89.3)	
IIIB	15 (10.6)	47 (5.6)		14 (10.2)	15 (10.7)	
Tumour stage, *n* (%)			0.294			0.036
T1	35 (24.6)	229 (27.2)		35 (25.5)	34 (24.3)	
T2	60 (42.3)	439 (52.2)		60 (43.8)	63 (45.0)	
T3	32 (22.5)	126 (15.0)		28 (20.4)	28 (20.0)	
T4	15 (10.6)	47 (5.6)		14 (10.2)	15 (10.7)	
LN examined, *n* (%)			0.237			0.023
0–9	68 (47.9)	305 (36.3)		64 (46.7)	67 (47.9)	
≥10	74 (52.1)	536 (63.7)		73 (53.3)	73 (52.1)	
LN positivity, *n* (%)			0.237			0.013
0–5	106 (74.6)	627 (74.6)		101 (73.7)	104 (74.3)	
≥6	36 (25.4)	214 (25.4)		36 (26.3)	36 (25.7)	

LN: lymph node; PSM: propensity score matching; SMD: standard mean difference.

[18]. Notably, all patients received three-dimensional treatment in the Pless study (2001–2012). Hence, we investigated whether the improvement of radiotherapy techniques would be accompanied by a better prognosis using recently updated real-world data (2010–2015). Regrettably, our findings are consistent with the findings of Pless study to some extent; in the Pless study, the whole group analysis revealed no significant difference in prognosis before and after matching. However, the differences were statistically significant before and after PSM in the lung SCC subgroups ($P = 0.000$ and $P = 0.043$, respectively). More encouragingly, some studies have shown that PrORT is an independent prognostic factor of OS in patients with stage IIIA-N2 NSCLC, and there is no obvious benefit in AC [19–21]. To some extent, this is consistent with our conclusions. The present study indicated that PrORT might confer survival benefits to patients with lung SCC and that different pathological types should not be treated equally.

In addition, some studies have shown that preoperative neoadjuvant radiotherapy can promote the release of tumour-associated antigens [22]. Neoadjuvant immunotherapy can enhance the initiation and activation of tumour antigen-driven T cells [23]. Moreover, neoadjuvant immunotherapy significantly improves the long-term OS or cure rates and reduces systemic recurrence in NSCLC [10]. Combined with the results of our study, we believe that PrORT combined with immunotherapy may be a better treatment for N2 NSCLC, especially lung SCC [24, 25].

The SEER database is a population-based oncology registry in the USA, covering ∼28% of the American population. It contains detailed clinical and prognostic data of hundreds of thousands of lung cancer cases since 1973. Generally speaking, analysis of NSCLC cases from the SEER database largely reduces selection bias [26, 27]. However, this study has some shortcomings such as the exploratory nature of the analyses, lack of functional data and important data (such as radiotherapy course and dose, chemotherapy regimen, side effects related to radiotherapy and chemotherapy, progression-free survival and DFS). In addition, the SEER database is a real-world pure management database in the USA, with limited general applicability, and the results need to be further verified by more prospective studies and clinical data. These factors may have affected our conclusions to some extent.

CONCLUSION

PrORT demonstrated an OS benefit for patients with stage N2 lung SCC; however, further prospective randomized clinical trials are warranted to confirm this finding.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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ETHICS STATEMENT

The patient information in the SEER database is publicly available and hence, our study was exempt from Ethics Review Committee approval. This study was conducted in compliance with the principles of the Declaration of Helsinki.

Conflict of interest: none declared.

Author contributions

Yunan Wang: Data curation; Formal analysis; Software; Writing—original draft. **Yunliang Cao:** Data curation; Formal analysis. **Mengjia Wu:** Formal analysis. **Yanyi Lu:** Investigation. **Bo He:** Methodology. **Lei Zhou:** Methodology. **Wei Hu:** Conceptualization; Data curation; Writing—original draft; Writing—review & editing.

Reviewer information

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