Original Article

Value of postoperative radiotherapy for stage IIIa-N2 non-small cell lung cancer: an analysis based on SEER database

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Background: The role of postoperative radiotherapy (PORT) in resected stage IIIa-N2 non-small cell lung cancer (NSCLC) patients who have received adjuvant chemotherapy remains controversial. This study aimed to explore the value of PORT and determine which patients could benefit from PORT.

Methods: Stage IIIa-N2 NSCLC patients treated with surgery and adjuvant chemotherapy were identified from the Surveillance, Epidemiology and End Results (SEER) databases from 2004 to 2015. Eligible patients were divided into the following two groups: PORT group and non-PORT group. Overall survival (OS) was estimated by the Kaplan-Meier (KM) method, and differences in survival were evaluated with log-rank test. Long-term cause-specific mortality consisted of lung cancer-related mortality and non-lung cancer-related mortality was investigated through competing risk analysis. Cox regression analysis was performed to identify variables that significantly affected OS.

Results: We identified 2,347 eligible patients, after propensity score matching (PSM), 877 pairs were selected. Overall, there was no significant difference in OS between two groups, but the patients who received PORT had a lower lung cancer-related mortality rate. Subgroup analysis showed that PORT was associated with a significantly better OS and lower lung cancer-related mortality rate in patients with T2, grade I–II and positive/resected lymph node ratio (LNR) ≥0.31. The non-lung cancer-related mortality of PORT group was higher in the patients with squamous cell carcinoma, although the difference was not significant. The independent prognostic factors for OS were age, sex, grade, histology, the American Joint Committee on Cancer (AJCC) T stage and LNR.

Conclusions: Our results revealed that PORT appears to be the optimal treatment strategy in patients with AJCC T2, grade I–II and LNR ≥0.31. PORT may not be recommended for patients with squamous cell carcinoma.

Keywords: Non-small cell lung cancer (NSCLC); postoperative radiotherapy (PORT); survival; Surveillance, Epidemiology and End Results (SEER) database

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Introduction

Lung cancer is the most common cancer and remains the leading cause of cancer-related mortality worldwide (1). Non-small cell lung cancer (NSCLC) is the most common type, accounting for 80–85% of lung cancer, and approximately 30% of these cases have been diagnosed with locally advanced disease (stage IIIA/IIIB) (2). Although there is a potential for cure, more than half of these patients have recurrence and metastasis, frequently resulting in death (3).

For operable stage IIIa-N2 NSCLC patients, the current standard treatment is surgical resection of the primary tumor and dissection of the mediastinal lymph node, combined with postoperative platinum-based adjuvant chemotherapy (4,5). Whether these patients can benefit from postoperative radiotherapy (PORT) remains controversial (6). The evidence supporting the recommending of PORT for these patients mainly comes from a retrospective analysis based on the nationally recognized National Cancer Database (NCDB) and the Surveillance, Epidemiology and End Results (SEER) database (7,8). Further supporting evidence came from the Adjuvant Navelbine International Trialist Association (ANITA) randomized trial data (9). However, these early studies had several important constraints, including the use of outdated radiation technology, inaccurate staging system and loose screening conditions. Therefore, the conclusions drawn have limited reliability and should not be used in a general way.

Another, more comprehensive, study does not support the use of PORT in these patients. As reported during the 2020 European Society for Medical Oncology conference, the Lung ART study (NCT00410683) is the first prospective randomized study in Europe to evaluate PORT following complete resection of N2 NSCLC (10). This study mainly involved patients who had received adjuvant chemotherapy. The primary endpoint was disease-free survival (DFS), and secondary endpoints were overall survival (OS), tumor recurrence, local control rate, incidence of second primary cancer and treatment-related toxicity. The results showed that PORT improved median DFS and chest disease control rate, which was consistent with previous reports. However, PORT did not significantly improve OS but did correlate with increased treatment-related side effects, suggesting that PORT should not be recommended as a standard treatment for such patients. Hui *et al.* (11) also demonstrated that patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy, PORT did not improve OS and DFS, while it only improve locoregional recurrence-free survival. It should be noted that neither of them did provide stratified results. Therefore, it is important to identify populations among stage IIIa-N2 NSCLC patients that may benefit from PORT.

Accordingly, we attempted to answer this question through a retrospective study of high-quality, population-based data. We analyzed data from the SEER databases to stratify impacts of PORT in the treatment regimen of stage IIIa-N2 NSCLC patients. Specifically, our study evaluated the impact of PORT on OS and long-term cause-specific mortality in patients with stage IIIa-N2 NSCLC to provide a basis for clinical decision-making. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2456/rc).

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Analysis of data from the SEER database does not require a medical ethics review or informed consent, as cancer is a publicly reported disease in the United States.

Patients

In this study, we obtain data from SEER 18 regs custom data (additional treatment field) and sub [1975–2016] database in November 2018. According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging (12), lung cancer patients from 2004 to 2015 were selected. The inclusion criteria: (I) patients with stage IIIa-N2 lung cancer who received adjuvant chemotherapy and surgery; (II) NSCLC that was pathologically proven (histologic types selected were coded as 8012, 8013, 8022, 8031, 8033, 8050, 8070 to 8072, 8074, 8082 to 8084, 8140, 8201, 8230, 8246, 8249, 8250 8252, 8253, 8255, 8260, 8310, 8323, 8341, 8480, 8481, 8490, 8507, 8550, 8560, 8570 and 8574); (III) NSCLC that was the only cancer or the first primary cancer. Exclusion criteria included: (I) missing or incomplete data; (II) the age is less than 18 years old; (III) the number of dissected lymph nodes was less than 6; (IV) patients without mediastinal lymph node dissection; (V) non-external radiotherapy; (VI) non-PORT; (VII) the survival

time was less than 1 month. Variables extracted from the SEER database included age at diagnosis, sex, pathologic grade, derived AJCC T stage, primary site labeled, SEER*Stat RX summary-surgery primary site, ICD-O-3 histology code and behavior, regional nodes examined, regional nodes positive, radiation recode, chemotherapy recode, Radiation sequence with surgery, vital status recode, cause of death (COD) to site rec Kaplan Meier (KM) and survival months. Finally, 2,347 patients were included, and we divided all the patients into two groups: the PORT group and the non-PORT group. Consistent with the definition in previous clinical trials, PORT was defined as all patients who received postoperative beam radiation therapy, whereas non-PORT was the opposite.

Variables and outcome

According to AJCC 8th edition staging system, we restaged all the patients as being stage IIIa-N2. The lymph node ratio (LNR) was defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes removed. Deng *et al.* demonstrated that 0.31 was the optimal cut-off value for evaluating the survival rate of LNR (13). They considered that patients with LNR <0.31 had better OS than those with LNR ≥0.31. Therefore, this study selects 0.31 as the dividing point of LNR grouping. The SEER database defined mortality data based on the International Classification of Diseases Revisions, long-term cause-specific mortality was divided into lung cancer-related mortality and non-lung cancer-related mortality. The causes of non-lung cancer-related mortality include: accidents and adverse reactions, respiratory diseases, blood system diseases, nervous system diseases, cardiovascular and cerebrovascular diseases, digestive system diseases, urinary system diseases, endocrine system diseases, various malignant tumors, suicide and self-mutilation. The time of OS and cancer-specific mortality was defined as the time from the date of diagnosis to the date of interesting death and the time of last follow-up, respectively.

Statistical analysis

R software (version 3.6.3) was used for statistical analyses, and P<0.05 (bilateral) was considered to indicate statistical significance. Propensity score matching (PSM) is to calculate the propensity score of each research object, and select individuals from the control group with the same or similar propensity scores as the treatment group to match, so as to balance the covariates between groups. The method treats each propensity score as an independent variable, making it evenly distributed between the control and treatment groups. This can achieve similar research results as randomized controlled trials and minimize bias. At present, this method has been widely used in observational studies and clinical studies with non-randomized data. In this study, the cases were matched by the "nearest" method based on propensity scores to reduce selection bias between baseline variables, including age, gender, grade, histology, AJCC T stage, laterality and LNR. The matching ratio is 1:1. The KM method was used to evaluate OS, and any differences in survival were evaluated with a stratified log-rank test. Long-term cause-specific mortality consisted of lung cancer-related mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) was investigated through competing risk analysis. Univariate and multivariate analyses were conducted by the cox regression model, in which the variables with statistical significance in univariate analysis would be included in multivariate analysis for further research.

Results

Patient characteristics

Before matching with propensity score, A total of 2,347 patients met inclusion criteria and exclusion criteria were included (*Figure 1*); 46.5% (1,092/2,347) cases underwent PORT. The median follow-up time was 35 months. More patients were over 65 years old (P=0.008) in the non-PORT group. In addition, the proportion of patients with LRN <0.31 was significantly higher in the non-PORT group (P<0.001). After matching with propensity score, 1,754 patients were selected (877 in the PORT group; 877 in the non-PORT group). There were no significant differences in baseline variates between the two groups (*Table 1*), indicating that the two groups had a good balance of variables after matching.

Survival analysis

There was no difference in OS and long-term cause specific mortality between PORT group and non-PORT group before matching (*Figure 2A,2B*). The median OS value of both groups was 51 months. The 1-, 3-, and 5-year OS values were 91.8%, 48.1% and 27.7% for the PORT group, 89.8% and 49.8%, and 28.0% for the non-PORT

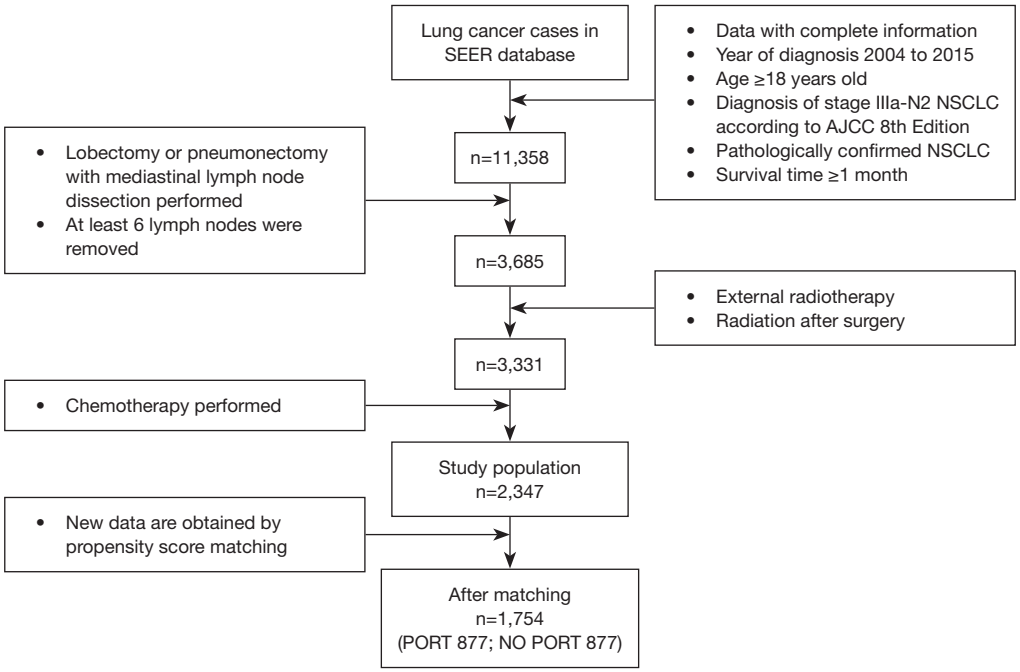

Figure 1 The flow diagram of the selection process for the study cohort. SEER, Surveillance, Epidemiology and End Results; NSCLC, non-small cell lung cancer; AJCC, American Joint Committee on Cancer; PORT, postoperative radiotherapy.

group, respectively. In the PORT group, the 1-, 3- and 5-year cancer-specific mortality consisted of lung cancer-related mortality (7.8%, 33.7%, and 44.2%) and non-lung cancer-related mortality (1.5%, 7.0%, and 10.9%). In the non-PORT group, the 1-, 3- and 5-year cancer-specific mortality consisted of lung cancer-related mortality (9.5%, 31.3%, and 45.1%) and non-lung cancer-related mortality (2.2%, 7.5%, and 11.6%).

After eliminating the covariate differences that may influence OS and long-term cause-specific mortality, we found that the PORT group did not have a significant improvement in OS compared with the non-PORT group (P=0.073) (*Figure 2C*), but the PORT group had significantly lower lung cancer-related mortality rate (P=0.047) (*Figure 2D*). The median follow-up time in PORT group and non-PORT group was 36 months and 35 months, respectively. The median OS values were 52 and 49 months for the PORT group and non-PORT group, respectively. The 1-, 3-, and 5-year OS values were 92.6%, 50.2% and 29.1% for the PORT group, and 90.2%, 49.8% and 28.4% for the non-PORT group, respectively. In the PORT group, the 1-, 3- and 5-year cancer-specific mortality consisted of lung cancer-related mortality (6.8%, 31.3%, and 42.6%) and non-lung cancer-related mortality (1.4%, 7.3%, and 11.5%). In the non-PORT group, the 1-, 3- and 5-year cancer-specific mortality consisted of lung cancer-related mortality (7.9%, 31.6%, and 45.8%) and non-lung cancer-related mortality (2.7%, 7.6%, and 11.2%).

Univariate and multivariate cox regression analysis was performed to identify variables that significantly affected OS before PSM matched (*Table 2*). The results showed that age (≥65 *vs.* <65, HR =1.33, P<0.001), sex (male *vs.* female, HR =1.242, P<0.001), Grade (III–IV *vs.* I–II, HR =1.147, P=0.0124), histology (others *vs.* adenocarcinomas, HR =1.228, P=0.0142; squamous cell neoplasms *vs.* adenocarcinomas, HR =1.18, P=0.0229), AJCC T stage (T2 *vs.* T1, HR =1.269, P<0.001) and LNR (≥0.31 *vs.* <0.31, HR =1.663, P<0.001) were significantly associated with OS (*Figure 3*). PORT (yes *vs.* no, HR, 0.936; 95% CI: 0.856 to 1.024; P=0.227) and laterality (right *vs.* left, HR, 0.930; 95% CI: 0.850 to 1.018; P=0.186) were not independent prognostic factors.

Subgroup analysis

In order to better describe the effect of PORT on the OS and long-term cause-specific mortality of NSCLC patients, we stratified the parameters of matched patients. PORT was

Table 1 Patient characteristics before and after propensity score matching

Characteristics	Before matching, n (%)			After matching, n (%)		
	PORT	Non-PORT	P value	PORT	Non-PORT	P value
Total number	1,092	1,255		877	877	
Age (years)						
<65	521 (47.7)	529 (42.2)	<0.01	392 (44.7)	392 (44.7)	1
≥65	571 (52.3)	726 (57.8)		485 (55.3)	485 (55.3)	
Sex						
Female	601 (55.0)	722 (57.5)	0.241	507 (57.8)	507 (57.8)	1
Male	491 (45.0)	533 (42.5)		370 (42.2)	370 (42.2)	
Grade						
I–II	593 (54.3)	691 (55.1)	0.745	485 (55.3)	485 (55.3)	1
III–IV	499 (45.7)	564 (44.9)		392 (44.7)	392 (44.7)	
Histology						
Adenocarcinomas	755 (69.1)	875 (69.7)	0.556	636 (72.5)	636 (72.5)	1
Squamous cell neoplasms	183 (16.8)	221 (17.6)		134 (15.3)	134 (15.3)	
Others	154 (14.1)	159 (12.7)		107 (12.2)	107 (12.2)	
AJCC T						
T1	413 (37.8)	513 (40.9)	0.142	315 (35.9)	315 (35.9)	1
T2	679 (62.2)	742 (59.1)		562 (64.1)	562 (64.1)	
Laterality						
Left	472 (43.2)	575 (45.8)	0.223	372 (42.4)	372 (42.4)	1
Right	620 (56.8)	680 (54.2)		505 (57.6)	505 (57.6)	
LNR						
<0.31	562 (51.5)	792 (63.1)	<0.001	497 (56.7)	497 (56.7)	1
≥0.31	530 (48.5)	463 (36.9)		380 (43.3)	380 (43.3)	

PORT, postoperative radiotherapy; AJCC, American Joint Committee on Cancer; LNR, lymph node ratio.

associated with a significantly better OS in AJCC T2, grade I–II and LNR ≥0.31 patients (*Figure 3A*,*3C*,*3E*). PORT also correlated with significantly lower rates of lung cancer-related mortality for these subgroups (*Figure 3B*,*3D*,*3F*). There was no significant difference in OS and lung cancer-specific mortality in AJCC T1, grade III–IV and LNR <0.31 patients (Figure S1).

We also observed that squamous cell carcinoma patients in the PORT group did exhibit higher non-lung cancer-related mortality, although the difference between the two groups was not significant (P=0.0716) (*Figure 4A*,*4B*). In addition, there were no significant differences in OS and cause-specific mortality when comparing patients by other factors, including age, sex, adenocarcinoma, other pathological types and laterality (Figures S2-S5).

Discussion

The curative effect of a single treatment for stage IIIa-N2 NSCLC is considered to be limited. Even if an operation results in complete resection (R0 resection), the probability of death from recurrence or metastasis within 5 years of the operation is still high (14). Therefore, it is important to explore the best treatment modes for this group. Whether

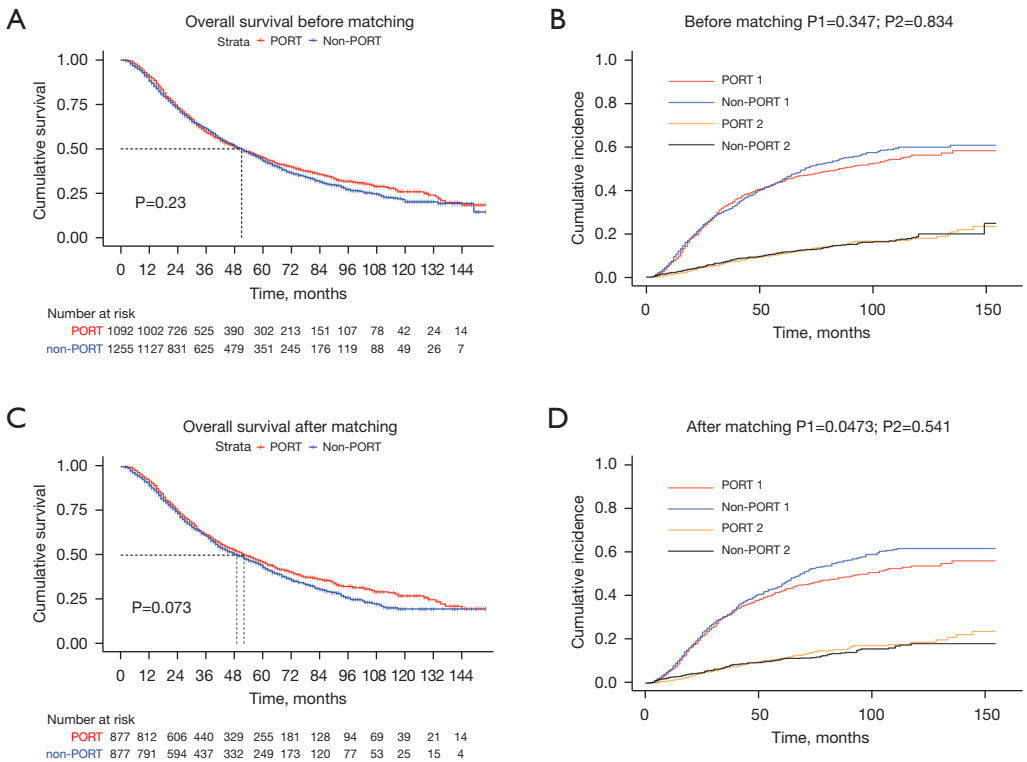

Figure 2 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group before and after PSM. (A) The overall survival between patients with PORT group and non-PORT group before PSM; (B) the cause-specific mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) between patients with PORT group and non-PORT group before PSM; (C) the overall survival between patients with PORT group and non-PORT group after PSM; (D) the cause-specific mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) between patients with PORT group and non-PORT group after PSM. PORT, postoperative radiotherapy; PSM, propensity score matching.

PORT will bring survival benefits to stage III a-N2 NSCLC patients is the focus of debate.

Many literatures have proved that that PORT could improve the local control rate of tumor by eliminating small residual lesions, and the loss of these lesions would ultimately translates into longer-term survival benefits (15-17). In 2006, Lally *et al.* reported that PORT can significantly improve the OS of patients with N2 lymph node disease, which suggested potentially positive effects of PORT on stage III a-N2 NSCLC patients (8). Therefore, National Comprehensive Cancer Network guidelines recommend PORT as the standard treatment for such patients. However, the result of this report was limited by the radiotherapy technology available at that time, and the sixth edition of the lung cancer staging system used in this study did not accurately reflect the prognosis of patients. Moreover, a large number of patients with incomplete resection were included because the screening conditions related to surgery were not strictly limited. Finally, the baseline level of the research subjects in this study were not balanced, which may have led to some bias. Therefore its conclusions may not be applicable in the present environment. As radiotherapy technology, lung cancer staging systems, operation and statistical methods advanced, potential benefits of PORT for patients with stage IIIa-N2 NSCLC deserved further analysis.

In this study, all patients in the current analysis were treated since from 2004 to 2015; therefore, it is a reasonable presumption that most would have been treated with modern techniques such as computed tomography simulation and at least linac-based, three-dimensional, conformal radiotherapy (RT). Using a large population-based registry of patients with resected stage IIIA (N2) NSCLC, we investigated the survival and long-term

Table 2 Univariate and multivariate Cox regression analysis of variables associated with overall survival for resected stage IIIa-N2 NSCLC patients who have received adjuvant chemotherapy before PSM

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<65	Reference		Reference	
≥65	1.342 (1.225–1.470)	<0.001	1.330 (1.214–1.457)	<0.001
Sex				
Female	Reference		Reference	
Male	1.249 (1.142–1.366)	<0.001	1.242 (1.133–1.361)	<0.001
Grade				
I–II	Reference		Reference	
III–IV	1.172 (1.072–1.282)	<0.01	1.147 (1.048–1.255)	0.0124
Histology				
Adenocarcinomas	Reference		Reference	
Squamous cell neoplasms	1.195 (1.064–1.343)	0.0119	1.180 (1.047–1.331)	0.0229
Others	1.200 (1.047–1.376)	0.0277	1.228 (1.070–1.409)	0.0142
AJCC T				
T1	Reference		Reference	
T2	1.271 (1.159–1.394)	<0.001	1.269 (1.157–1.393)	<0.001
Laterality				
Left	Reference			
Right	0.930 (0.850–1.018)	0.186		
LNR				
<0.31	Reference		Reference	
≥0.31	1.607 (1.469–1.758)	<0.001	1.663 (1.519–1.821)	<0.001
PORT				
No	Reference			
Yes	0.936 (0.856–1.024)	0.227		

NSCLC, non-small cell lung cancer; PSM, propensity score matching; HR, hazard ratio; AJCC, American Joint Committee on Cancer; LNR, lymph node ratio; PORT, postoperative radiotherapy.

cause-specific mortality of 2,347 patients based on the 8th edition of AJCC/TNM staging system. PSM was used to balance the baseline covariates before comparing the OS and cause-specific mortality between two groups. Pairing eliminated significant differences in variables that might have significant impacts on survival rates (18,19). Our results suggest no improvement in OS with PORT compared with adjuvant chemotherapy alone, but lung cancer-related mortality was significantly lower in the PORT group. In addition, univariate and multivariate cox regression analysis shows that PORT wasn't an independent prognostic factor for such patients. To sum up, PORT should not be recommended as a standard treatment for resected stage IIIa-N2 NSCLC patients who have received adjuvant chemotherapy. This is consistent with the main conclusions of the lung-art study. However, looking at the

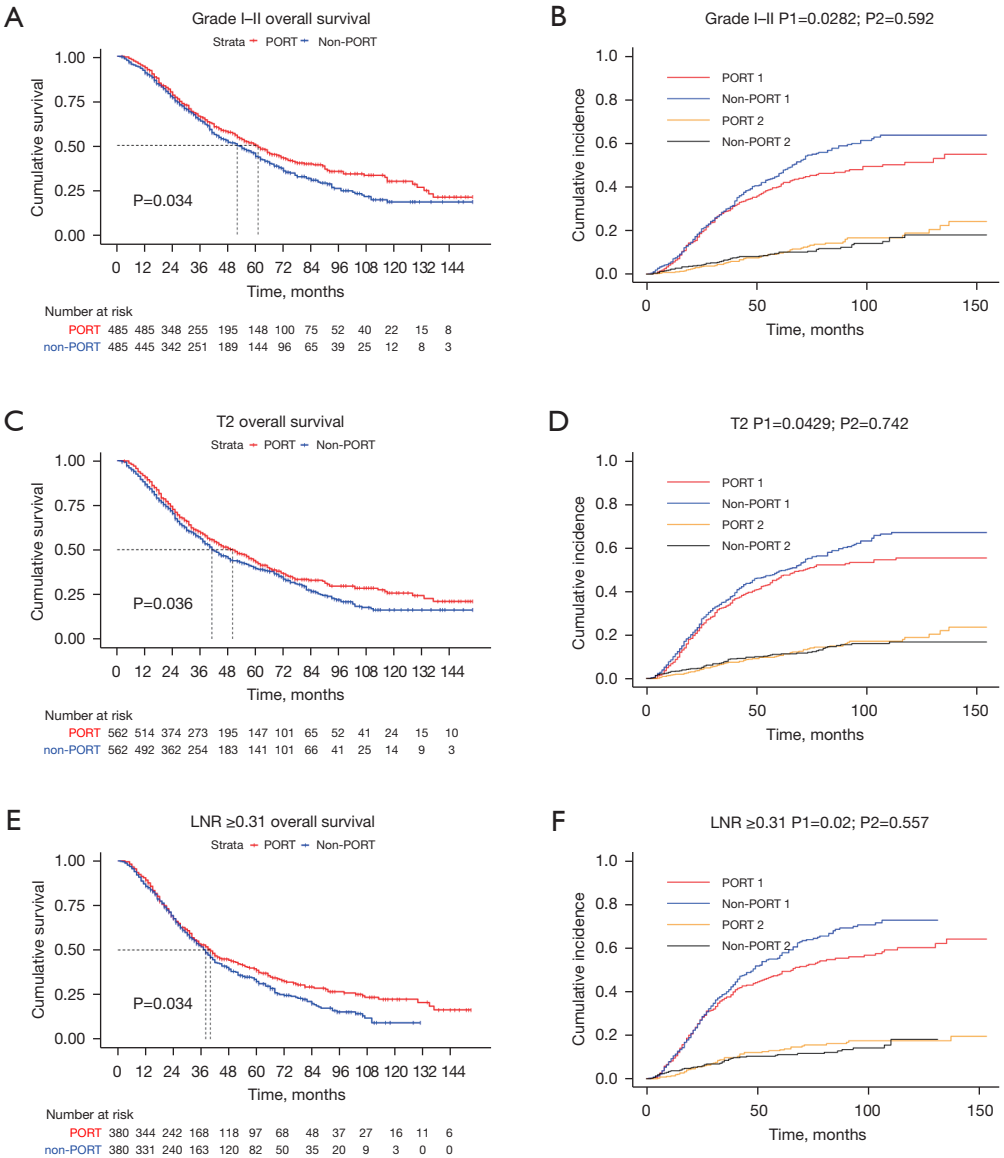

Figure 3 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in Grade I–II, T2 and LNR ≥0.31 after PSM. (A) the overall survival between PORT group and non-PORT group in Grade I–II patients; (B) the cause-specific mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) between PORT group and non-PORT group in Grade I–II patients; (C) the overall survival between PORT group and non-PORT group in T2 patients; (D) the cause-specific mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) between PORT group and non-PORT group in T2 patients; (E) the overall survival between PORT group and non-PORT group in LNR ≥0.31 patients; (F) the cause-specific mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) between PORT group and non-PORT group in LNR ≥0.31 patients. PORT, postoperative radiotherapy; PSM, propensity score matching; LNR, lymph node ratio.

specific values of each observation endpoint, it will be found that the performance of 3-year/5-year OS in this study, whether in PORT Group (48.1%/27.7% *vs.* 66.5%/55%) or non-PORT group (49.8%/28% *vs.* 68.5%/55%), is lower than that in lung-art study. This is because patients with incomplete resection were included in this study. Nevertheless, there was still no statistical difference in OS between the two groups in our study, which further

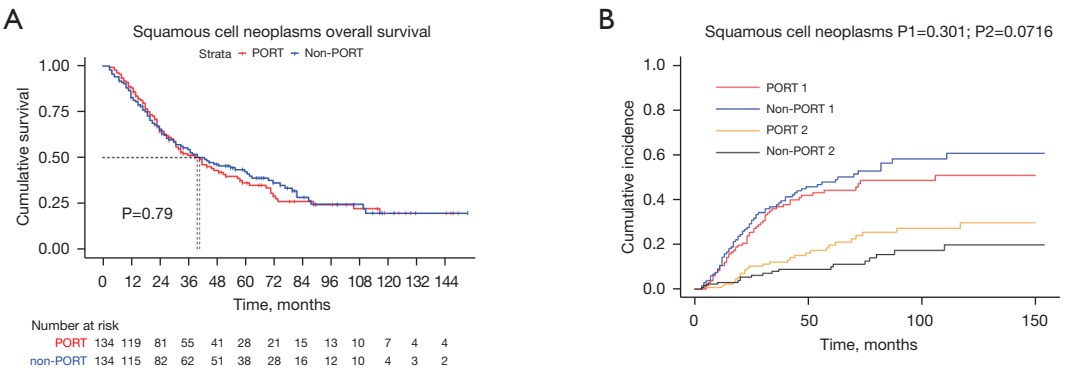

Figure 4 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in squamous cell carcinoma after PSM. (A) The overall survival between PORT group and non-PORT group in squamous cell carcinoma patients; (B) the cause-specific mortality (PORT 1 and non-PORT 1) and non-lung cancer-related mortality (PORT 2 and non-PORT 2) between PORT group and non-PORT group in squamous cell carcinoma patients. PORT, postoperative radiotherapy; PSM, propensity score matching.

confirmed the main results of lung art study.

To further identify the subgroups of patients who may benefit from PORT, we stratified the patients. The result shows that the PORT group had better OS and lower lung cancer-related mortality rate in patients with LNR ≥0.31, which is consistent with the results reported by Deng *et al.* (13). Interestingly, we found for the first time that PORT significantly improved OS and reduced lung cancer-related mortality in patients with AJCC T2 and grade I–II, while there was no significant difference in OS and lung cancer-related mortality in patients with AJCC T1 and grade III–IV. We believe that the main reason why radiotherapy plays little role in AJCC T1 NSCLC is that AJCC T1 patients have small tumor volume, do not invade visceral pleura and main bronchus, and are less likely to invade tumor blood vessels and nerves. Although grade III–IV tumors are more malignant, the patients do not tend to experience an OS benefit from PORT. The underlying cause may be that these tumors grow too fast and lack sufficient blood supply, which leads to decreased of radio-sensitivity due to hypoxia. In addition, squamous cell carcinoma patients in the PORT group have higher non-lung cancer-related mortality than those in the non-PORT group. As most patients with squamous cell carcinoma are long-term smokers, and the proportion of patients with chronic cardiovascular or respiratory diseases is large. These morbidities tend to increase the incidence of radiotherapy-related complications, potentially leading to the higher non-lung cancer-related mortality (20,21). Our study provided a more detailed categorization of patients with stage IIIa-N2 disease who benefited from PORT, and our findings suggest that patients with stage N2 undergoing PORT should be carefully selected.

There are several noteworthy limitations in this study. First, the patient's chronic diseases (including chronic obstructive pulmonary disease and diabetes, etc.) is an important prognostic factor for lung cancer patients receiving PORT. These comorbidities can increase PORT-related complications and may lead to reduced survival; second, the SEER database does not provide relevant information on the completion rate of treatment which may affect the prognosis; third, the factors such as the sequence of radiotherapy and adjuvant chemotherapy, the number of cycles of chemotherapy, the types of chemotherapy drugs and the incidence of adverse events related to treatment may also affect the survival rate of patients. But the SEER database lacks relevant information; fourth, due to the limitations of SEER database, we cannot further describe the recurrence sites of PORT group and non-PORT group, so we cannot verify the effectiveness of radiotherapy in preventing thoracic lymph node recurrence. Therefore, we will add our own corresponding data on tumor radiotherapy and chemotherapy in subsequent articles. Fifth, Previous literature reported that extralymphatic invasion may be one of the high-risk factors for postoperative recurrence and metastasis of NSCLC (22). We also consider extralymphatic invasion as a factor in the analysis. However, due to the lack of relevant information in SEER database, we cannot further analyze it; Sixth, due to the increasing use of targeted therapy and immunotherapy in lung adenocarcinoma, the survival rates of patients receiving targeted therapy may be significantly different from those

not receiving targeted therapy. The Prophet database also lacks information on these treatments. However, patients with stage III A-N2 NSCLC are less likely to receive such therapy postoperatively, so our results may not be materially affected; Seventh, there are no data include surgeon experience, surgical volume and surgical methods (e.g., open or video-assisted thoracic surgery) in the SEER database. Finally, our research is retrospective, and some biases are inevitable. A larger randomized cohort of prospective studies is needed.

Conclusions

In conclusion, analysis of the SEER database shows that PORT offers a significant survival benefit for patients with AJCC T2, grade I–II cancers and LNR ≥0.31. There was also a detrimental effect when PORT was administered to patients with squamous cell carcinoma. In order to extend and verify our results, large-scale prospective studies are warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2456/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2456/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2456/coif). All authors report that this work was supported by the National Natural Science Foundation of China (Grant No. 81972852). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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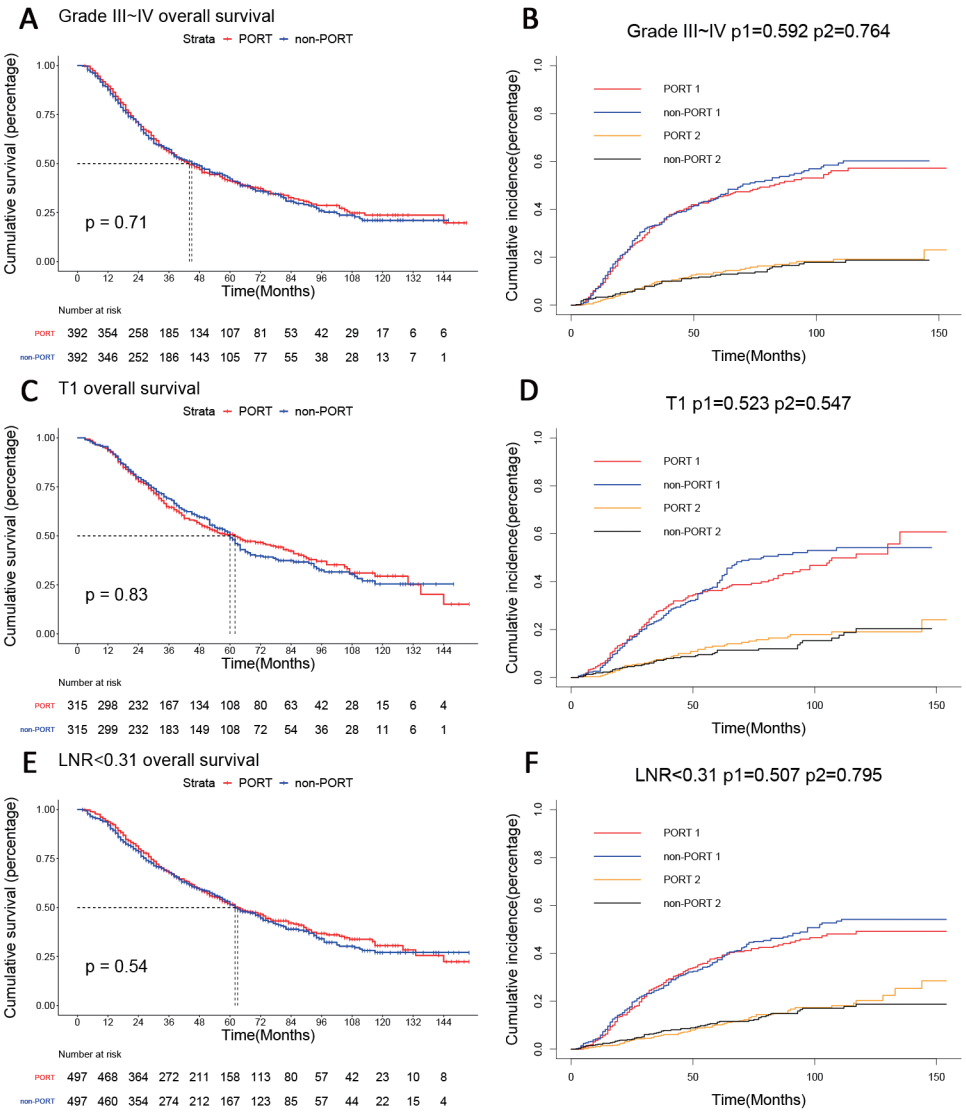

Figure S1 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in Grade III-IV, T1 and LNR <0.31 after PSM. (A) the overall survival between PORT group and non-PORT group in Grade III-IV patients; (B) the cause-specific mortality between PORT group and non-PORT group in Grade III-IV patients; (C) the overall survival between PORT group and non-PORT group in T1 patients; (D) the cause-specific mortality between PORT group and non-PORT group in T1 patients; (E) the overall survival between PORT group and non-PORT group in LNR <0.31 patients; (F) the cause-specific mortality between PORT group and non-PORT group in LNR <0.31 patients. PORT, postoperative radiotherapy; PSM, propensity score matching; LNR, lymph node ratio.

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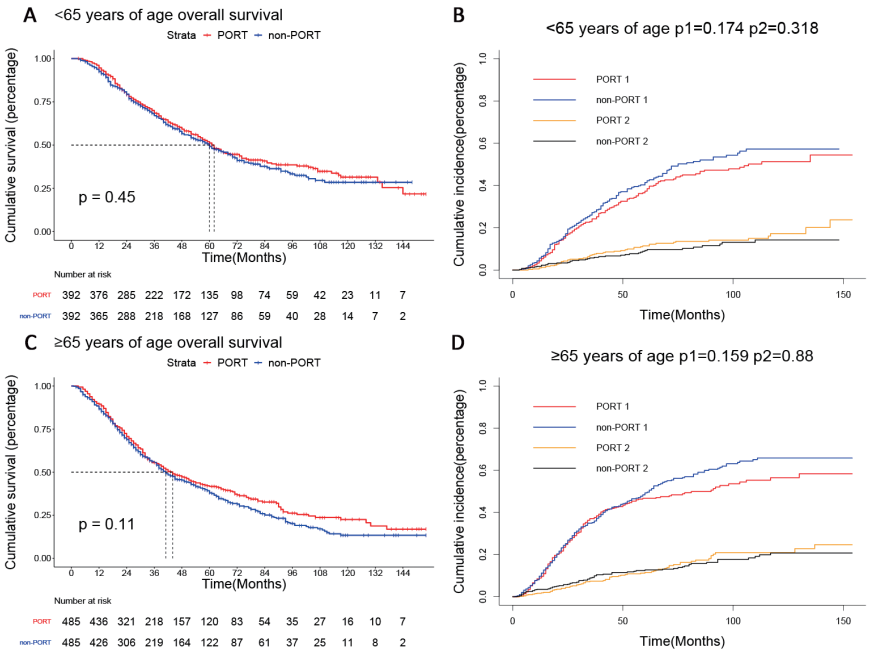

Figure S2 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in <65 years of age and ≥65 years of age after PSM. (A) the overall survival between patients with PORT group and non-PORT group in <65 years of age; (B) the cause-specific mortality between PORT group and non-PORT group in <65 years of age; (C) the overall survival between PORT group and non-PORT group in ≥65 years of age; (D) the cause-specific mortality between PORT group and non-PORT group in ≥65 years of age. PORT, postoperative radiotherapy; PSM, propensity score matching.

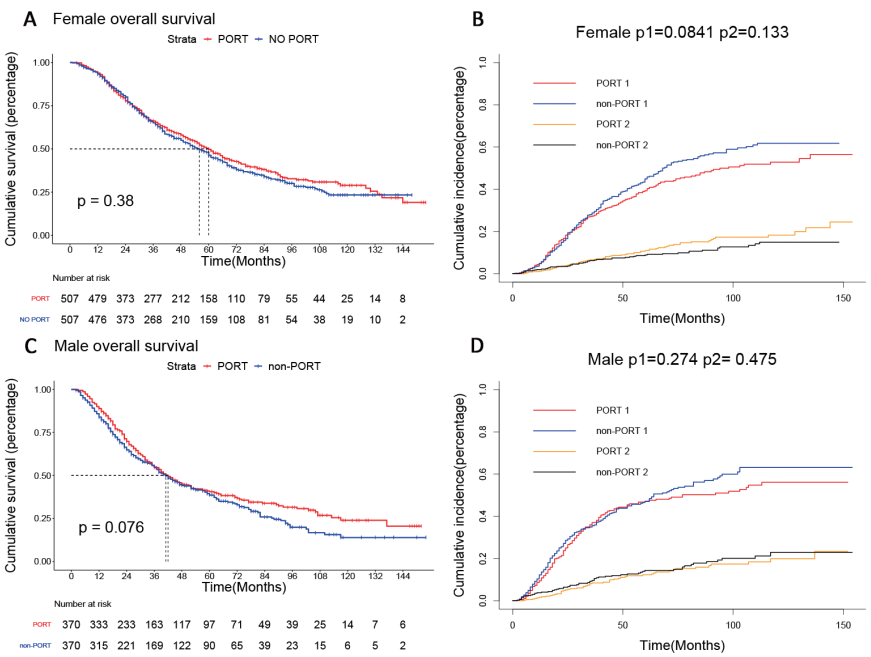

Figure S3 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in female and male after PSM. (A) the overall survival between patients with PORT group and non-PORT group in female; (B) the cause-specific mortality between PORT group and non-PORT group in female; (C) the overall survival between PORT group and non-PORT group in male; (D) the cause-specific mortality between PORT group and non-PORT group in male. PORT, postoperative radiotherapy; PSM, propensity score matching.

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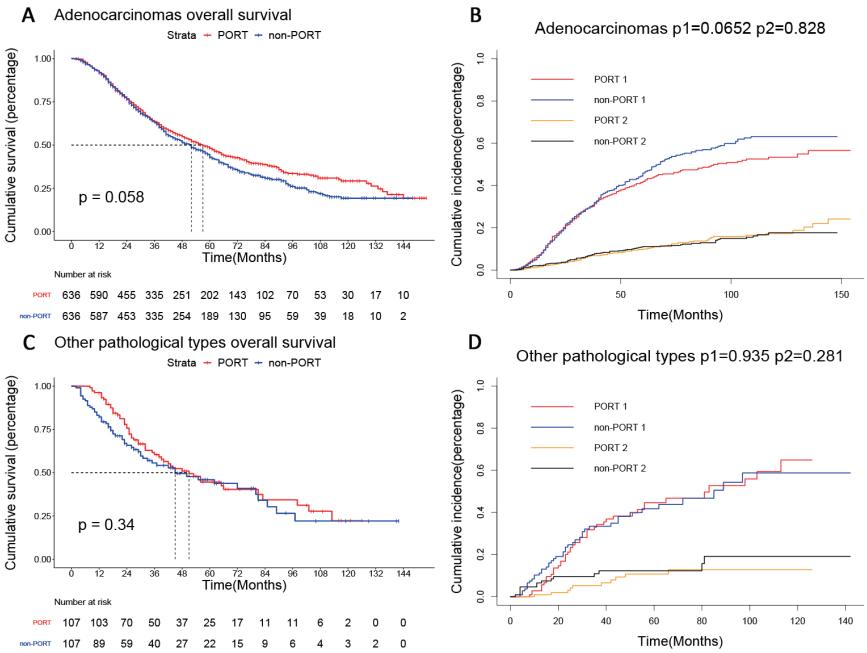

Figure S4 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in adenocarcinomas and other pathological types after PSM. (A) the overall survival between patients with PORT group and non-PORT group in adenocarcinomas; (B) the cause-specific mortality between PORT group and non-PORT group in adenocarcinomas; (C) the overall survival between PORT group and non-PORT group in other pathological types; (D) the cause-specific mortality between PORT group and non-PORT group in other pathological types. PORT, postoperative radiotherapy; PSM, propensity score matching.

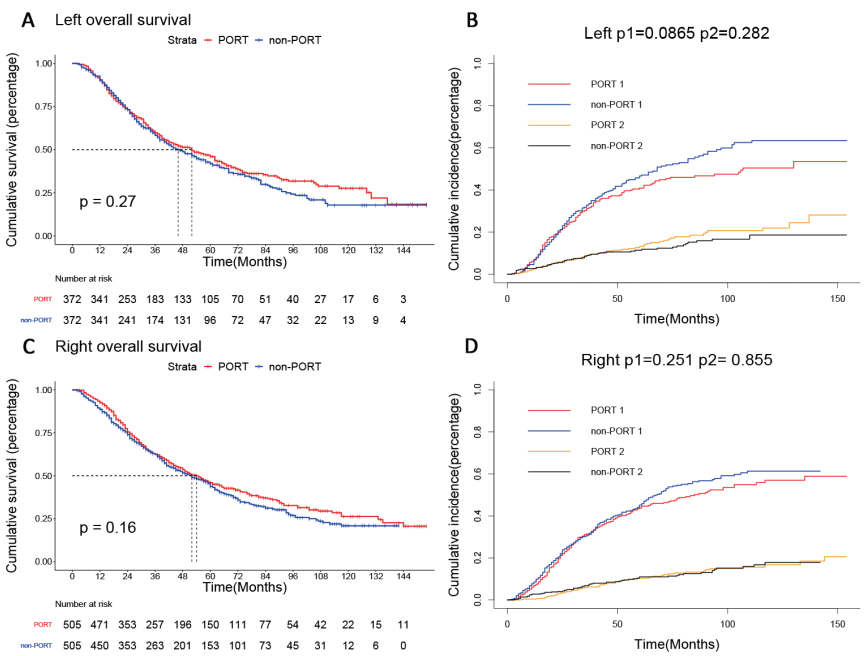

Figure S5 Overall survival and cause-specific mortality between patients with PORT group and non-PORT group in left and right lung after PSM. (A) the overall survival between patients with PORT group and non-PORT group in left lung; (B) the cause-specific mortality between PORT group and non-PORT group in left lung; (C) the overall survival between PORT group and non-PORT group in right lung; (D) the cause-specific mortality between PORT group and non-PORT group in right lung. PORT, postoperative radiotherapy; PSM, propensity score matching.

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